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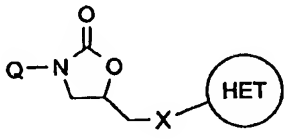
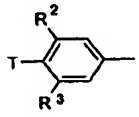


(I)



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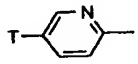

(Q2)

(57) Abstract

Compounds of formula (I), or a pharmaceutically–acceptable salt, or an in–vivo–hydrolysable ester thereof, wherein, for example, X is –O– or –S–; HET is an optionally substituted C–linked 6–membered heteroaryl ring containing 1 or 2 N atoms; Q is selected from, for example, (Q1) and (Q2); R^2 and R^3 are independently hydrogen or fluoro; T is selected from a range of groups, for example, an N–linked (fully unsaturated) 5–membered heteroaryl ring system or a 3,6–dihydro–(2H)–pyran–4–yl group or a 4–substituted piperazino group; are useful as antibacterial agents; and processes for their manufacture and pharmaceutical compositions containing them are described.

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OXAZOLIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing a substituted oxazolidinone ring. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded primarily as effective against Gram-positive pathogens because of their particularly good activity against such pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant Streptococcus pneumoniae and multiply resistant Enterococcus faecium.

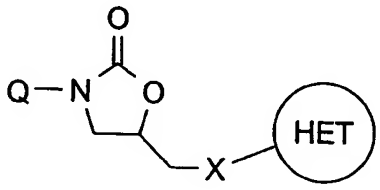
The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with nephrotoxicity and ototoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens.

Certain antibacterial compounds containing an oxazolidinone ring have been described in the art (for example, Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165). Such antibacterial oxazolidinone compounds with a 5-methylacetamide sidechain may be subject to mammalian peptidase metabolism. Furthermore, bacterial resistance to known antibacterial agents may develop, for

example, by (i) the evolution of active binding sites in the bacteria rendering a previously active pharmacophore less effective or redundant, and/or (ii) the evolution of means to chemically deactivate a given pharmacophore. Therefore, there remains an ongoing need to find new antibacterial agents with a favourable pharmacological profile, in particular for compounds containing new pharmacophores.

We have discovered a class of antibiotic compounds containing a new class of substituted oxazolidinone ring which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams.

Accordingly the present invention provides a compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

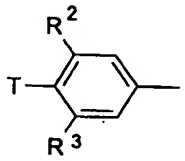


(I)

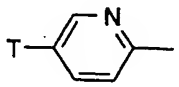
wherein X is -O- or -S-;

HET is a C-linked 6-membered heteroaryl ring containing 1 or 2 N, which ring is optionally substituted on any available C atom (provided that when the N atom is adjacent to the X-link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

Q is selected from Q1 to Q9 :-



Q1



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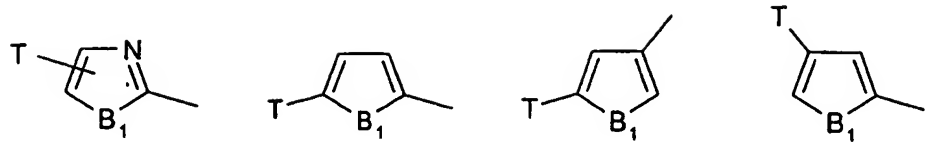
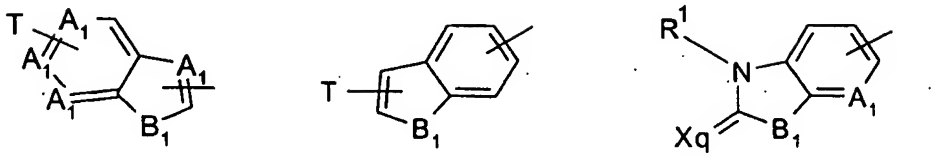


Q3 Q4 Q5 Q6



Q7 Q8 Q9

wherein R^2 and R^3 are independently hydrogen or fluoro;

wherein A_1 is carbon or nitrogen; B_1 is O or S (or, in Q9 only, NH); X_q is O, S or N-R^1 (wherein R^1 is hydrogen, (1-4C)alkyl or hydroxy-(1-4C)alkyl); and wherein in Q7 each A_1 is independently selected from carbon or nitrogen, with a maximum of 2 nitrogen heteroatoms in the 6-membered ring, and Q7 is linked to T via any of the A_1 atoms (when A_1 is carbon), and linked in the 5-membered ring via the specified carbon atom, or via A_1 when A_1 is carbon; Q8 is linked toT via either of the specified carbon atoms in the 5-membered ring, and linked in the benzo-ring via either of the two specified carbon atoms on either side of the linking bond shown; and Q9 is linked via either of the two specified carbon atoms on either side of the linking bond shown;

wherein T is selected from the groups in (TA) to (TD) below (wherein AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 are defined hereinbelow);

(TA) T is selected from the following groups :-

(TAa) AR1, AR1-(1-4C)alkyl-, AR2 (carbon linked), AR3;

(TAb) AR1-CH(OH), AR2-CH(OH)-, AR3-CH(OH)-;

(TAc) AR1-CO-, AR2-CO-, AR3-CO-, AR4-CO-;

(TAd) AR1-O-, AR2-O-, AR3-O-;

(TAe) AR1-S(O)$_q$- , AR2-S(O)$_q$- , AR3-S(O)$_q$- (q is 0, 1 or 2);

(TAf) an optionally substituted N-linked (fully unsaturated) 5-membered heteroaryl ring system containing 1, 2 or 3 nitrogen atoms;

(TAg) a carbon linked tropol-3-one or tropol-4-one, optionally substituted in a position not adjacent to the linking position; or

(TB) T is selected from the following groups :-

(TBa) halo or (1-4C)alkyl

{optionally substituted by one or more groups each independently selected from hydroxy, (1-4C)alkoxy, (1-4C)alkanoyl, cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, -NRvRw, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2), CY1, CY2 or AR1};

(TBb) -NRv^{1}Rw^1 ;

(TBc) ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl;

(TBd) R^{10}CO- , R^{10}S(O)$_q$- (q is 0, 1 or 2) or R^{10}CS-

wherein R^{10} is selected from the following groups :-

(TBda) CY1 or CY2;

(TBdb) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl, -NRvRw, ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl or 2-(AR2)ethenyl; or

(TBdc) (1-4C)alkyl {optionally substituted as defined in (TBa) above, or by (1-4C)alkylS(O)$_p$NH- or (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N- (p is 1 or 2)};

wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl; Rv^1 is hydrogen, (1-4C)alkyl or (3-8C)cycloalkyl; Rw^1 is hydrogen, (1-4C)alkyl, (3-8C)cycloalkyl, (1-4C)alkyl-CO- or (1-4C)alkylS(O)$_q$- (q is 1 or 2); or

(TC) T is selected from the following groups :-

(TCa) an optionally substituted, fully saturated 4-membered monocyclic ring containing 1

heteroatom selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or sp^3 carbon atom;

(TCb) an optionally substituted 5-membered monocyclic ring containing 1 heteroatom selected from O, N and S (optionally oxidised), and linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom, which monocyclic ring is fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(TCc) an optionally substituted 6- or 7-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom, which monocyclic ring is fully saturated other than (where appropriate) at a linking sp^2 carbon atom; or

(TD) T is selected from the following groups :-

(TDa) a bicyclic spiro-ring system containing 0, 1 or 2 ring nitrogen atoms as the only ring heteroatoms, the structure consisting of a 5- or 6-membered ring system (linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom) substituted (but not adjacent to the linking position) by a 3-, 4- or 5-membered spiro-carbon-linked ring; which bicyclic ring system is

(i) fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(ii) contains one -N(Rc)- group in the ring system (at least two carbon atoms away from the linking position when the link is via a nitrogen atom or an sp^2 carbon atom) or one -N(Rc)- group in an optional substituent (not adjacent to the linking position) and is

(iii) optionally further substituted on an available ring carbon atom; or

(TDb) a 7-, 8- or 9-membered bicyclic ring system (linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom) containing 0, 1 or 2 ring nitrogen atoms (and optionally a further O or S ring heteroatom), the structure containing a bridge of 1, 2 or 3 carbon atoms; which bicyclic ring system is

(i) fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(ii) contains one O or S heteroatom, or one -N(Rc)- group in the ring (at least two carbon atoms away from the linking position when the link is via a nitrogen atom or an sp^2 carbon atom) or one -N(Rc)- group in an optional substituent (not adjacent to the linking position) and is

(iii) optionally further substituted on an available ring carbon atom;

wherein Rc is selected from groups (Rc1) to (Rc5) :-

(Rc1) (1-6C)alkyl {optionally substituted by one or more (1-4C)alkanoyl groups (including geminal disubstitution) and/or optionally monosubstituted by cyano, (1-4C)alkoxy, trifluoromethyl, (1-4C)alkoxycarbonyl, phenyl (optionally substituted as for AR defined hereinafter), (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2); or, on any but the first carbon atom of the (1-6C)alkyl chain, optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy and fluoro, and/or optionally monosubstituted by oxo, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylS(O)$_p$NH- or (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N- (p is 1 or 2)};

(Rc2) $R^{13}CO-$, $R^{13}SO_2-$ or $R^{13}CS-$

wherein R^{13} is selected from (Rc2a) to (Rc2e) :-

(Rc2a) AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1, CY2;

(Rc2b) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, 2-(AR2a)ethenyl;

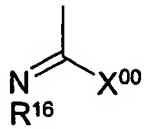
(Rc2c) (1-10C)alkyl {optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkanoyl and amino; and/or optionally substituted by one group selected from phosphonate [phosphono, -P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], phosphoryl [-O-P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylaminocarbonyl, di((1-4C)alkyl)aminocarbonyl, (1-4C)alkylS(O)$_p$NH-, (1-

4C)alkylS(O)$_p$-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)$_p$NH-, fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-, (1-4C)alkylS(O)$_q$-, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-, AR1-S(O)$_q$- , AR2-S(O)$_q$- , AR3-S(O)$_q$- , AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups};

(Rc2d) $R^{14}C(O)O(1\text{-}6C)$alkyl wherein R^{14} is AR1, AR2, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (Rc2c)};

(Rc2e) $R^{15}O$- wherein R^{15} is benzyl, (1-6C)alkyl {optionally substituted as defined for (Rc2c)}, CY1, CY2 or AR2b;

(Rc3) hydrogen, cyano, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, or of the formula **(Rc3a)**



(Rc3a)

wherein X^{00} is $-OR^{17}$, $-SR^{17}$, $-NHR^{17}$and $-N(R^{17})_2$;

wherein R^{17} is hydrogen (when X^{00} is $-NHR^{17}$and $-N(R^{17})_2$), and R^{17} is (1-4C)alkyl, phenyl or AR2 (when X^{00} is $-OR^{17}$, $-SR^{17}$ and $-NHR^{17}$); and R^{16} is cyano, nitro, (1-4C)alkylsulfonyl, (4-7C)cycloalkylsulfonyl, phenylsulfonyl, (1-4C)alkanoyl and (1-4C)alkoxycarbonyl;

(Rc4) trityl, AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b;

(Rc5) RdOC(Re)=CH(C=O)-, RfC(=O)C(=O)-, RgN=C(Rh)C(=O)- or RiNHC(Rj)=CHC(=O)- wherein Rd is (1-6C)alkyl; Re is hydrogen or (1-6C)alkyl, or Rd and Re together form a (3-4C)alkylene chain; Rf is hydrogen, (1-6C)alkyl, hydroxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkyl, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-4C)alkylamino(2-6C)alkoxy, di-(1-4C)alkylamino(2-6C)alkoxy; Rg is (1-6C)alkyl, hydroxy or (1-6C)alkoxy; Rh is hydrogen or (1-6C)alkyl; Ri is hydrogen, (1-6C)alkyl, AR1, AR2, AR2a, AR2b and Rj is hydrogen or (1-6C)alkyl;

wherein

AR1 is an optionally substituted phenyl or optionally substituted naphthyl;

AR2 is an optionally substituted 5- or 6-membered, fully unsaturated (i.e with the maximum degree of unsaturation) monocyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised;

AR2a is a partially hydrogenated version of AR2 (i.e. AR2 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom if the ring is not thereby quaternised;

AR2b is a fully hydrogenated version of AR2 (i.e. AR2 systems having no unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom;

AR3 is an optionally substituted 8-, 9- or 10-membered, fully unsaturated (i.e with the maximum degree of unsaturation) bicyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

AR3a is a partially hydrogenated version of AR3 (i.e. AR3 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in either of the rings comprising the bicyclic system;

AR3b is a fully hydrogenated version of AR3 (i.e. AR3 systems having no unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom, in either of the rings comprising the bicyclic system;

AR4 is an optionally substituted 13- or 14-membered, fully unsaturated (i.e with the maximum degree of unsaturation) tricyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in any of the rings comprising the tricyclic system;

AR4a is a partially hydrogenated version of AR4 (i.e. AR4 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in any of the rings comprising the tricyclic system;

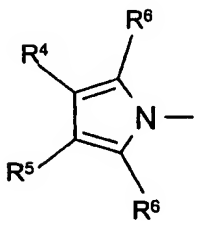
CY1 is an optionally substituted cyclobutyl, cyclopentyl or cyclohexyl ring;

CY2 is an optionally substituted cyclopentenyl or cyclohexenyl ring.

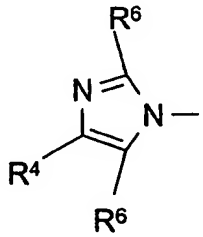
In this specification, where it is stated that a ring may be linked via an sp^2 carbon atom, which ring is fully saturated other than (where appropriate) at a linking sp^2 carbon atom, it is to be understood that the ring is linked via a C=C double bond.

In another emdodiment, (Rc1) is as defined above other than the optional phenyl substituent on (1-6C)alkyl is optionally substituted as for AR1 defined hereinafter; and (Rc2c), is as defined above and further includes carboxy as an optional substituent on R^{13} as (1-10C)alkyl.

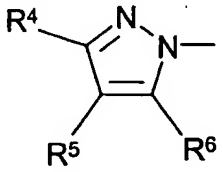
(TAf) When T is an optionally substituted N-linked (fully unsaturated) 5-membered heteroaryl ring system containing 1, 2 or 3 nitrogen atoms, it is preferably selected from a group of formula (TAf1) to (TAf6) below (particularly (TAf1), (TAf2), (TAf4) and (TAf5), and especially (TAf1) and/or (TAf2)). The above preferred values of (TAf) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.



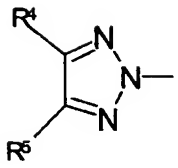
(TAf1)



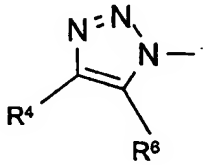
(TAf2)



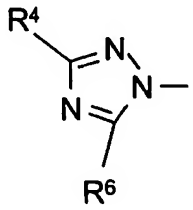
(TAf3)



(TAf4)



(TAf5)



(TAf6)

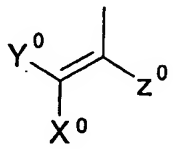
wherein :

R^6 is selected (independently where appropriate) from hydrogen, (1-4C)alkyl, (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, carbamoyl and cyano;

R^4 and R^5 are independently selected from hydrogen, halo, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (1-4C)alkylS(O)q- (q is 0, 1 or 2), (1-4C)alkanoyl, (1-4C)alkoxycarbonyl, (2-4C)alkanoyloxy-(1-4C)alkyl, benzoxy-(1-4C)alkyl, (2-4C)alkanoylamino, -CONRvRw, -NRvRw and (1-4C)alkyl {optionally substituted by hydroxy, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (1-4C)alkylS(O)q- (q is 0, 1 or 2), (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONRvRw, -NRvRw; wherein RvRw is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl};

or R^4 is selected from one of the groups in (TAfa) to (TAfc) below, or (where appropriate) one of R^4 and R^5 is selected from the above list of R^4 and R^5 values, and the other is selected from one of the groups in (TAfa) to (TAfc) below :-

(TAfa) a group of the formula (TAfa1)



(TAfa1)

wherein Z^0 is hydrogen or (1-4C)alkyl;

X^0 and Y^0 are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxycarbonyl, halo, cyano, nitro, (1-4C)alkylS(O)q- (q is 0, 1 or 2), RvRwNSO$_2$-, trifluoromethyl, pentafluoroethyl, (1-4C)alkanoyl and -CONRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]; or

one of X^0 and Y^0 is selected from the above list of X^0 and Y^0 values, and the other is selected from phenyl, phenylcarbonyl, -S(O)$_q$-phenyl (q is 0, 1 or 2), N-(phenyl)carbamoyl, phenylaminosulfonyl, AR2, (AR2)-CO-, (AR2)-S(O)q- (q is 0, 1 or 2), N-(AR2)carbamoyl and (AR2)aminosulfonyl; wherein any phenyl group in (TAfa) may be optionally substituted by up to three substituents independently selected from (1-4C)alkyl, cyano, trifluoromethyl, nitro, halo and (1-4C)alkylsulfonyl;

(TAfb) an acetylene of the formula -≡-H or -≡-(1-4C)alkyl;

(TAfc) -X^1-Y^1-AR2, -X^1-Y^1-AR2a, -X^1-Y^1-AR2b, -X^1-Y^1-AR3, -X^1-Y^1-AR3a or -X^1-Y^1-AR3b;

wherein X^1 is a direct bond or -CH(OH)- and

Y^1 is $-(CH_2)_m-$, $-(CH_2)_n-NH-(CH_2)_m-$, $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$, $-C(=S)NH-(CH_2)_m-$ or $-C(=O)O-(CH_2)_m-$;

or wherein X^1 is $-(CH_2)_n-$ or $-CH(Me)-(CH_2)_m-$ and

Y^1 is $-(CH_2)_m-NH-(CH_2)_m-$, $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$, $-C(=S)NH-(CH_2)_m-$, $-C(=O)O-(CH_2)_m-$ or $-S(O)_q-(CH_2)_m-$;

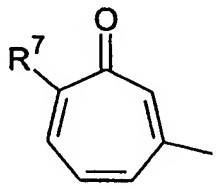
or wherein X^1 is $-CH_2O-$, $-CH_2NH-$ or $-CH_2N((1\text{-}4C)alkyl)-$ and

Y^1 is $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$ or $-C(=S)NH-(CH_2)_m-$; and additionally Y^1 is $-SO_2-$ when X^1 is $-CH_2NH-$ or $-CH_2N((1\text{-}4C)alkyl)-$, and Y^1 is $-(CH_2)_m-$ when X^1 is $-CH_2O-$ or $-CH_2N((1\text{-}4C)alkyl)-$; wherein n is 1, 2 or 3; m is 0, 1, 2 or 3 and q is 0, 1 or 2; and when Y^1 is $-(CH_2)_m-NH-(CH_2)_m-$ each m is independently selected from 0, 1, 2 or 3.

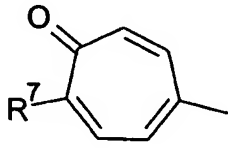
It is to be understood that when a value for $-X^1-$ is a two-atom link and is written, for example, as $-CH_2NH-$ it is the left hand part ($-CH_2-$ here) which is bonded to the group of formula (TAf1) to (TAf6) and the right hand part (-NH- here) which is bonded to $-Y^1-$ in the definition in (TAfc). Similarly, when $-Y^1-$ is a two-atom link and is written, for example, as -CONH- it is the left hand part of $-Y^1-$ (-CO- here) which is bonded to the right hand part of $-X^1-$, and the right hand part of $-Y^1-$ (-NH- here) which is bonded to the AR2, AR2a, AR2b, AR3, AR3a or AR3b moiety in the definition in (TAfc).

Preferably R^6 is hydrogen or (1-4C)alkyl, and R^4 and R^5 are independently selected from hydrogen, (1-4C)alkyl or one of R^4 and R^5 is selected from group (TAfa). Other preferable substituents on the (TAf1) to (TAf6) are illustrated in the accompanying Examples.

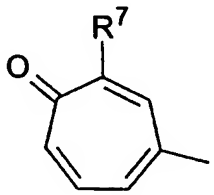
(TAg) When T is a carbon linked tropol-3-one or tropol-4-one, optionally substituted in a position not adjacent to the linking position **(TAg)**, it is preferably selected from a group of formula (TAg1), (TAg2) or (TAg3). The above preferred values of (TAg) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.



(TAg1)



(TAg2)



(TAg3)

wherein R^7 is selected from

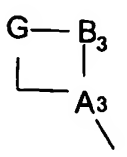
(TAga) hydrogen, (1-4C)alkyl {optionally substituted by one or two substituents (excluding geminal disubstitution) independently selected from fluoro, hydroxy, (1-4C)alkoxy and -NRvRw]}; or

(TAgb) R^8-O-, R^8-S-, R^8-NH- or R^8R^8-N-;

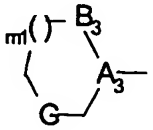
wherein R^8 is selected (independently where appropriate) from hydrogen, (1-4C)alkyl or (3-8C)cycloalkyl {both optionally substituted by one or two substituents (excluding geminal disubstitution) independently selected from hydroxy, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and -NRvRw}, (2-4C)alkenyl {optionally substituted by one or two -NRvRw substituents}, (1-4C)alkanoyl {optionally substituted by one or two substituents independently selected from -NRvRw and hydroxy}, phenyl-(1-4C)alkyl or pyridyl-(1-4C)alkyl {the phenyl and pyridyl (preferably pyridin-4-yl) rings being optionally substituted by one or two -NRvRw substituents}; or

(TAgc) morpholino, thiomorpholino, pyrrolidino {optionally independently substituted in the 3- and/or 4-positions by (1-4C)alkyl}, piperidino substituted in the 4-position by R^9-, R^9-O-, R^9-S-, R^9-NH- or R^9R^9-N-; wherein R^9 is selected (independently where appropriate) from hydrogen, (1-4C)alkyl {optionally substituted by one or two (excluding geminal disubstitution) hydroxy, (1-4C)alkoxy, (1-4C)alkoxycarbonyl or -NRvRw} and piperazino {optionally substituted in the 4-position by (1-4C)alkyl, (3-8C)cycloalkyl, (1-4C)alkanoyl, (1-4C)alkoxycarbonyl or (1-4C)alkylsulfonyl, and optionally independently substituted in the 3- and/or 5-positions by (1-4C)alkyl}; wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl.

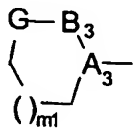
(TC) Preferred values for the optional substituents and groups defined in (TCa) to (TCc) are defined by formulae (TC1) to (TC4) :-



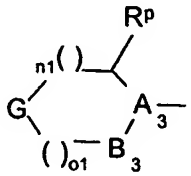
(TC1)



(TC2)



(TC3)



(TC4)

wherein in (TC1) : $>A_3-B_3-$ is >C(Rq)-CH(Rr)- and G is -O-, -S-, -SO-, $-SO_2-$ or >N(Rc);

wherein in (TC2) : m1 is 0, 1 or 2; $>A_3-B_3-$ is >C=C(Rr)- or >C(Rq)-CH(Rr)- and G is -O-, -S-, -SO-, $-SO_2-$ or >N(Rc);

wherein in (TC3) : m1 is 0, 1 or 2; $>A_3-B_3-$ is >C(Rq)-CH(Rr)- (other than when Rq and Rr are both together hydrogen) and G is -O-, -S-, -SO-, $-SO_2-$ or >N(Rc);

wherein in (TC4) : n1 is 1 or 2; o1 is 1 or 2 and n1 + o1 = 2 or 3; $>A_3-B_3-$ is >C=C(Rr)- or >C(Rq)-CH(Rr)- or $>N-CH_2-$ and G is -O-, -S-, -SO-, $-SO_2-$ or >N(Rc); Rp is hydrogen, (1-4C)alkyl (other than when such substitution is defined by $>A_3-B_3-$), hydroxy, (1-4C)alkoxy or (1-4C)alkanoyloxy;

wherein in (TC1), (TC2) and (TC4); m1, n1 and o1 are as defined hereinbefore :

$>A_3-B_3-$ is $>N-CH_2-$ and G is $>C(R^{11})(R^{12})$, >C=O, >C-OH, >C-(1-4C)alkoxy, >C=N-OH, >C=N-(1-4C)alkoxy, >C=N-NH-(1-4C)alkyl, $>C=N-N((1-4C)alkyl)_2$ (the last two (1-4C)alkyl groups above in G being optionally substituted by hydroxy) or >C=N-N-CO-(1-4C)alkoxy; wherein > represents two single bonds;

Rq is hydrogen, hydroxy, halo, (1-4C)alkyl or (1-4C)alkanoyloxy;

Rr is (independently where appropriate) hydrogen or (1-4C)alkyl;

R^{11} is hydrogen, (1-4C)alkyl, fluoro(1-4C)alkyl, (1-4C)alkyl-thio-(1-4C)alkyl or hydroxy-(1-4C)alkyl and R^{12} is $-[C(Rr)(Rr)]_{m2}-N(Rr)(Rc)$ wherein m2 is 0, 1 or 2;

and, other than the ring substitution defined by G, $>A_3-B_3-$ and Rp, each ring system may be optionally further substituted on a carbon atom not adjacent to the link at $>A_3-$ by up to two substituents independently selected from (1-4C)alkyl, fluoro(1-4C)alkyl (including trifluoromethyl), (1-4C)alkyl-thio-(1-4C)alkyl, hydroxy-(1-4C)alkyl, amino, amino-(1-4C)alkyl, (1-4C)alkanoylamino, (1-4C)alkanoylamino-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, AR-oxymethyl, AR-thiomethyl, oxo (=O) (other than when G is >N-Rc and Rc is group **(Rc2)** defined hereinbefore) or independently selected from Rc; and also hydroxy or halo (the last two optional substituents only when G is -O- or -S-);

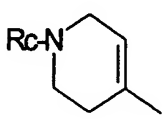
wherein AR is as defined for formula (IP) hereinafter; Rc is selected from groups (Rc1) to (Rc5) defined hereinbefore.

For the avoidance of doubt, $(\,)_{m1}$, $(\,)_{n1}$ and $(\,)_{o1}$ indicate $(-CH_2-)_{m1}$, $(-CH_2-)_{n1}$ and $(-CH_2-)_{o1}$ respectively (optionally substituted as described above).

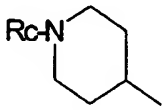
In the above definition of (TC1) to (TC4) and of the further optional substituents, AR

is preferably AR2, and the further optional substituents are preferably not selected from the values listed for Rc. A preferred value for G is >N(Rc) or >C(R^{11})(R^{12}).

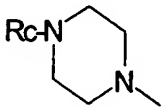
Particularly preferred values for the optional substituents and groups defined in (TCa) to (TCc), and (TC1) to (TC4) are contained in the following definitions (TC5) to (TC11) :-



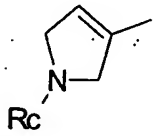
(TC5)



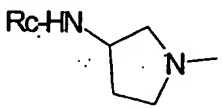
(TC6)



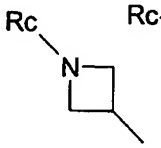
(TC7)



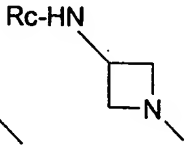
(TC8)



(TC9)



(TC10)



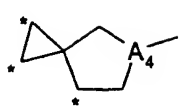
(TC11)

wherein Rc has any of the values listed hereinbefore or hereinafter.

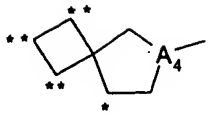
Especially preferred are (TC5), (TC6), (TC7) and (TC9), most especially (TC5) in which Rc has any of the values listed hereinbefore or hereinafter (especially $R^{13}CO$- with the preferable R^{13} values given hereinafter). In (TC5) Rc is preferably selected from the group (Rc2), especially $R^{13}CO$- with the preferable R^{13} values given hereinafter. In (TC7) Rc is preferably selected from group (Rc3) or (Rc4).

The above preferred values of (TCa) to (TCc) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.

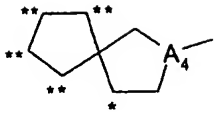
(TDa) When T is a bicyclic spiro-ring system as defined in (TDa), it is preferably selected from a group of formula (TDa1) to (TDa9). The above preferred values of (TDa) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.



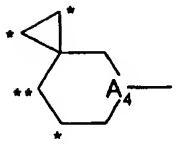
(TDa1)



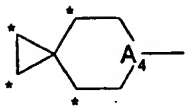
(TDa2)



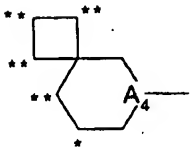
(TDa3)



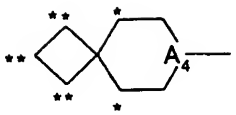
(TDa4)



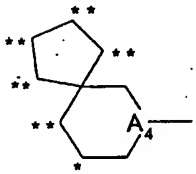
(TDa5)



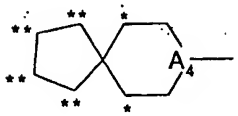
(TDa6)



(TDa7)



(TDa8)



(TDa9)

wherein;

(i) the A_4 linking group is a nitrogen atom or an sp^3 or sp^2 carbon atom (with the double bond, where appropriate, orientated in either direction); and

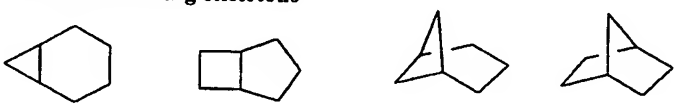
(ii) one of the ring carbon atoms at positions marked * and ** is replaced by one of the following groups -NRc-, >CH-NHRc, >CH-NRc-(1-4C)alkyl, >CH-CH_2-NHRc, >CH-CH_2-NRc-(1-4C)alkyl [wherein a central -CH_2- chain link is optionally mono- or di-substituted by (1-4C)alkyl]; with the provisos that positions marked * are not replaced by -NH- in the ring containing the A_4 link when A_4 is a nitrogen atom or an sp^2 carbon atom, and that positions marked * are not replaced by -NH- in the three membered ring in (TDa1), (TDa4) and (TDa5); and

(iii) the ring system is optionally (further) substituted on an available ring carbon atom by up to two substituents independently selected from (1-4C)alkyl, fluoro(1-4C)alkyl (including trifluoromethyl), (1-4C)alkyl-thio-(1-4C)alkyl, hydroxy-(1-4C)alkyl, amino, amino-(1-4C)alkyl, (1-4C)alkanoylamino, (1-4C)alkanoylamino-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, AR2-oxymethyl, AR2-thiomethyl, oxo (=O) (other than when the ring contains an >N-Rc and Rc is group **(Rc2)**) and also hydroxy or halo;

wherein Rc has any of the values listed hereinbefore or hereinafter.

(TDb) When T is a 7-, 8- or 9-membered bicyclic ring system containing a bridge of 1, 2 or 3 carbon atoms as defined in (TDb), it is preferably selected from a group defined by the ring skeletons shown in formulae (TDb1) to (TDb14) :-

7-membered ring skeletons



[4,1,0] (TDb1) [3,2,0] (TDb2) [3,1,1] (TDb3) [2,2,1] (TDb4)

8-membered ring skeletons

[3,3,0] (TDb5) [4,2,0] (TDb6) [4,1,1] (TDb7) [3,2,1] (TDb8) [2,2,2] (TDb9)

9-membered ring skeletons

[4,3,0] (TDb10) [5,2,0] (TDb11) [4,2,1] (TDb12) [3,3,1] (TDb13) [3,2,2] (TDb14)

wherein;

(i) the ring system contains 0, 1 or 2 ring nitrogen atoms (and optionally a further O or S ring heteroatom),and when present the ring nitrogen, O or S heteroatom/s are at any position other than as part of the 3-membered ring in (TDb1);

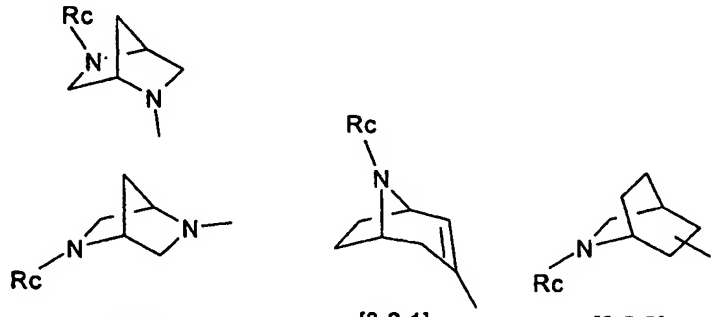
(ii) the ring system is linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom (with the double bond, where appropriate, orientated in either direction) from any position in either ring [other than from a bridgehead position or from an sp^2 carbon atom in the 4-membered ring in (TDb2), (TDb6) and (TDb11)];

(iii) one of the ring carbon atoms at a position not adjacent to the linking position, is replaced (other than when the ring contains an O or S heteroatom) by one of the following groups -NRc- [not at a bridgehead position], >C(H)-NHRc, >C(H)-NRc-(1-4C)alkyl, >C(H)-CH_2-NHRc, >C(H)-CH_2-NRc-(1-4C)alkyl [wherein the hydrogen atom shown in brackets is not present when the replacement is made at a bridgehead position and wherein a central -CH_2- chain link is optionally mono- or di-substituted by (1-4C)alkyl]; with the proviso that when the ring system is linked via a ring nitrogen atom or an sp^2 carbon atom any replacement of a ring carbon atom by -NRc-, O or S is at least two carbon atoms away from the linking position; and

(iv) the ring system is optionally (further) substituted on an available ring carbon atom as for the bicyclic spiro-ring systems described in (TDa); wherein Rc has any of the values listed hereinbefore or hereinafter.

It will be appreciated that unstable anti-Bredt compounds are not contemplated in this definition (i.e. compounds with stuctures (TDb3), (TDb4), (TDb7), (TDb8), (TDb9), (TDb12), (TDb13) and (TDb14) in which an sp^2 carbon atom is directed towards a bridgehead position).

Particularly preferred values of (TDb) are the following structures of formula (TDb4), (TDb8) and/or (TDb9); wherein Rc has any of the values listed hereinbefore or hereinafter. The above preferred values of (TDb) are particularly preferred when present in Q1 or Q2, especially Q1, and when X is -O-.

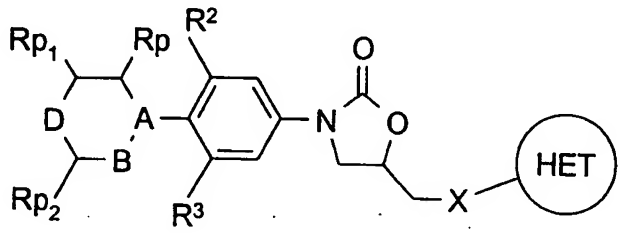


[2,2,1] (TDb4a & b) [3,2,1] (TDb8) [2,2,2] (TDb9)

In another embodiment there is provided a compound of the formula (I) which is defined by the formula (IP) below, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein

X is -O- or -S-;

HET is a C-linked 6-membered heteroaryl ring containing 1 or 2 N,(with the proviso that pyrimidin-2-yl is excluded), which ring is optionally substituted on any available C atom (provided that when the N atom is adjacent to the X-link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy and halogen;



(IP)

wherein: R^2 and R^3 are independently hydrogen or fluoro;

Rp is hydrogen, (1-4C)alkyl, hydroxy, (1-4C)alkoxy or (2-4C)alkanoyloxy;

>A-B- is of the formula >C=C(Rr)- , >CHCHRr- , >C(OH)CHRr- or >N-CH_2-

(> represents two single bonds) wherein Rr is hydrogen or (1-4C)alkyl;

D is -O-, -S-, -SO-, -SO_2- or >NRcp;

Rp1 and Rp2 are independently oxo (=O) [but not when Rcp is group **(PC)** below], (1-4C)alkyl, (1-4C)alkanoylamino-(1-4C)alkyl, hydroxy-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, AR-oxymethyl, AR-thiomethyl (wherein AR is as defined hereinbelow) or independently as defined for Rcp hereinbelow with the proviso that Rp1 and Rp2 are not phenyl, benzyl, AR (as defined hereinbelow), a tetrazole ring system, cyclopentyl or cyclohexyl; and when D is -O- or -S-, Rp1 and Rp2 are additionally independently hydroxy or bromo;

wherein Rcp is selected from (PA) to (PE) below :-

(PA) hydrogen, cyano, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl;

(PB) phenyl, benzyl, AR (as defined hereinbelow) or a tetrazole ring system [optionally mono-substituted in the 1- or 2- position of the tetrazole ring by (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl or (1-4C)alkanoyl] wherein the tetrazole ring system is joined to the nitrogen in >NRcp by a ring carbon atom;

(PC) $R^{13p}CO-$, $R^{13p}SO_2-$ or $R^{13p}CS-$ wherein R^{13p} is selected from (PCa) to (PCf) :-

(PCa) AR (as defined hereinbelow);

(PCb) cyclopentyl or cyclohexyl, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl or 1,4-dioxan-2-yl [optionally mono- or di-substituted by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), hydroxy (but excluding 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl or 1,4-dioxan-2-yl substituted by hydroxy), (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano and trifluoromethyl];

(PCc) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl, amino, (1-4C)alkylamino, di((1-4C)alkyl)amino, 2-(5- or 6-membered heteroaryl)ethenyl, 2-(5- or 6-membered (partially) hydrogenated heteroaryl)ethenyl, 2-phenylethenyl [wherein the heteroaryl or phenyl substituent is optionally substituted on an available carbon atom by up to three substituents independently selected from (1-4C)alkoxy, halo, cyano and (for the phenyl substituent only) (1-4C)alkylsulfonyl];

(PCd) (1-10C)alkyl [optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy and amino, or optionally monosubstituted by cyano, halo, (1-10C)alkoxy, trifluoromethyl, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(2-6C)alkanoylamino, (1-4C)alkylS(O)$_p$NH-, (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)$_p$NH-, fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-, phosphono, (1-4C)alkoxy(hydroxy)phosphoryl, di-(1-4C)alkoxyphosphoryl, (1-4C)alkylS(O)$_q$-, phenyl, naphthyl, phenoxy, naphthoxy, phenylamino, naphthylamino, phenylS(O)$_q$-, naphthylS(O)$_q$- [wherein said phenyl and naphthyl groups are optionally substituted by up to three substituents independently selected from (1-4C)alkoxy, halo and cyano], or CY (as defined hereinbelow), wherein p is 1 or 2 and q is 0, 1 or 2];

(PCe) $R^{14p}C(O)O(1-6C)alkyl$ wherein R^{14p} is an optionally substituted 5- or 6-membered heteroaryl, optionally substituted phenyl, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or optionally substituted (1-10C)alkyl;

(PCf) $R^{15p}O-$ wherein R^{15p} is benzyl or optionally substituted (1-6C)alkyl;

(PD) RdOC(Re)=CH(C=O)-, RfC(=O)C(=O)-, RgN=C(Rh)C(=O)- or RiNHC(Rj)=CHC(=O)- wherein Rd is (1-6C)alkyl; Re is hydrogen or (1-6C)alkyl, or Rd and

Re together form a (3-4C)alkylene chain; Rf is hydrogen, (1-6C)alkyl, hydroxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkyl, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-4C)alkylamino(2-6C)alkoxy, di-(1-4C)alkylamino(2-6C)alkoxy; Rg is (1-6C)alkyl, hydroxy or (1-6C)alkoxy; Rh is hydrogen or (1-6C)alkyl; Ri is hydrogen, (1-6C)alkyl, optionally substituted phenyl or an optionally substituted 5- or 6-membered heteroaryl [and (partially) hydrogenated versions thereof] and Rj is hydrogen or (1-6C)alkyl;

(PE) $R^{16p}CH(R^{17p})(CH_2)mp$- wherein mp is 0 or 1; R^{17p} is fluoro, cyano, (1-4C)alkoxy, (1-4C)alkylsulfonyl, (1-4C)alkoxycarbonyl or hydroxy, (provided that when mp is 0, R^{17p} is not fluoro or hydroxy) and R^{16p} is hydrogen or (1-4C)alkyl;

wherein AR is optionally substituted phenyl, optionally substituted phenyl(1-4C)alkyl, optionally substituted naphthyl, optionally substituted 5- or 6-membered heteroaryl; wherein AR is also an optionally substituted 5/6 or 6/6 bicyclic heteroaryl ring system, in which the bicyclic heteroaryl ring systems may be linked via an atom in either of the rings comprising the bicyclic system, and wherein both the mono- and bicyclic heteroaryl ring systems are linked via a ring carbon atom and may be (partially) hydrogenated;

wherein CY is selected from :-

(i) cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl or cyclohexenyl ring;

(ii) 5- or 6-membered heteroaryl, 5- or 6-membered heteroaryloxy, 5- or 6-membered heteroaryl-$S(O)_q$-, 5- or 6-membered heteroarylamino [and (partially) hydrogenated versions thereof] and

(iii) 5/6 or 6/6 bicyclic heteroaryl, 5/6 or 6/6 bicyclic heteroaryloxy, 5/6 or 6/6 bicyclic heteroaryl-$S(O)_q$-, 5/6 or 6/6 bicyclic heteroarylamino [and (partially) hydrogenated versions thereof]; wherein q is 0, 1 or 2 and any of the afore-mentioned ring systems in CY may be optionally substituted by up to three substituents independently selected from halo, (1-4C)alkyl [including geminal disubstitution when CY is a cycloalkyl or cycloalkenyl ring in (i)], acyl, oxo and nitro-(1-4C)alkyl.

For the avoidance of doubt, phosphono is $-P(O)(OH)_2$; (1-4C)alkoxy(hydroxy)-phosphoryl is a mono-(1-4C)alkoxy derivative of $-O-P(O)(OH)_2$; and di-(1-4C)alkoxyphosphoryl is a di-(1-4C)alkoxy derivative of $-O-P(O)(OH)_2$.

In this embodiment of formula (IP) a '5- or 6-membered heteroaryl' and 'heteroaryl

(monocyclic) ring' means a 5- or 6-membered aryl ring wherein (unless stated otherwise) 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen and sulfur. Unless stated otherwise, such rings are fully aromatic. Particular examples of 5- or 6-membered heteroaryl ring systems are furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole and thiophene.

In this embodiment of formula (IP) a '5/6 or 6/6 bicyclic heteroaryl ring system' and 'heteroaryl (bicyclic) ring' means an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring, the bicyclic ring system containing 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise, such rings are fully aromatic. Particular examples of 5/6 and 6/6 bicyclic ring systems are indole, benzofuran, benzimidazole, benzothiophene, benzisothiazole, benzoxazole, benzisoxazole, pyridoimidazole, pyrimidoimidazole, quinoline, quinoxaline, quinazoline, phthalazine, cinnoline and naphthyridine.

Particular optional substituents for alkyl, phenyl (and phenyl containing moieties) and naphthyl groups and ring carbon atoms in heteroaryl (mono or bicyclic) rings in R^{14p}, R^{15p}, Ri and AR include halo, (1-4C)alkyl , hydroxy, nitro, carbamoyl, (1-4C)alkylcarbamoyl, di-((1-4C)alkyl)carbamoyl, cyano, trifluoromethyl, trifluoromethoxy, amino, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-4C)alkyl $S(O)_q$- (q is 0, 1 or 2), carboxy, (1-4C)alkoxycarbonyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkanoyl, (1-4C)alkoxy, (1-4C)alkyl$S(O)_2$amino, (1-4C)alkanoylamino, benzoylamino, benzoyl, phenyl (optionally substituted by up to three substituents selected from halo, (1-4C)alkoxy or cyano), furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, thiophene, hydroxyimino(1-4C)alkyl, (1-4C)alkoxyimino(1-4C)alkyl, hydroxy-(1-4C)alkyl, halo-(1-4C)alkyl, nitro(1-4C)alkyl, amino(1-4C)alkyl, cyano(1-4C)alkyl, (1-4C)alkanesulfonamido, aminosulfonyl, (1-4C)alkylaminosulfonyl and di-((1-4C)alkyl)aminosulfonyl. The phenyl and naphthyl groups and heteroaryl (mono- or bicyclic) rings in R^{14p}, Ri and AR may be mono- or di-substituted on ring carbon atoms with substituents independently selected from the above list of particular optional substituents.

In this specification the term 'alkyl' includes straight chained and branched structures. For example, (1-6C)alkyl includes propyl, isopropyl and tert-butyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chained version only, and

references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. A similar convention applies to other radicals, for example halo(1-4C)alkyl includes 1-bromoethyl and 2-bromoethyl.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter.

Examples of **(1-4C)alkyl** and **(1-5C)alkyl** include methyl, ethyl, and propyl and isopropyl; examples of **(1-6C)alkyl** include methyl, ethyl, propyl, isopropyl, pentyl and hexyl; examples of **(1-10C)alkyl** include methyl, ethyl, propyl, isopropyl, pentyl, hexyl, heptyl, octyl and nonyl; examples of **(1-4C)alkanoylamino-(1-4C)alkyl** include formamidomethyl, acetamidomethyl and acetamidoethyl; examples of **hydroxy(1-4C)alkyl** and **hydroxy(1-6C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; examples of **(1-4C)alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **2-((1-4C)alkoxycarbonyl)ethenyl** include 2-(methoxycarbonyl)ethenyl and 2-(ethoxycarbonyl)ethenyl; examples of **2-cyano-2-((1-4C)alkyl)ethenyl** include 2-cyano-2-methylethenyl and 2-cyano-2-ethylethenyl; examples of **2-nitro-2-((1-4C)alkyl)ethenyl** include 2-nitro-2-methylethenyl and 2-nitro-2-ethylethenyl; examples of **2-((1-4C)alkylaminocarbonyl)ethenyl** include 2-(methylaminocarbonyl)ethenyl and 2-(ethylaminocarbonyl)ethenyl; examples of **(2-4C)alkenyl** include allyl and vinyl; examples of **(2-4C)alkynyl** include ethynyl and 2-propynyl; examples of **(1-4C)alkanoyl** include formyl, acetyl and propionyl; examples of **(1-4C)alkoxy** include methoxy, ethoxy and propoxy; examples of **(1-6C)alkoxy** and **(1-10C)alkoxy** include methoxy, ethoxy, propoxy and pentoxy; examples of **(1-4C)alkylthio** include methylthio and ethylthio; examples of **(1-4C)alkylamino** include methylamino, ethylamino and propylamino; examples of **di-((1-4C)alkyl)amino** include dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino and dipropylamino; examples of **halo** groups include fluoro, chloro and bromo; examples of **(1-4C)alkylsulfonyl** include methylsulfonyl and ethylsulfonyl; examples of **(1-4C)alkoxy-(1-4C)alkoxy** and **(1-6C)alkoxy-(1-6C)alkoxy** include methoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy and 3-methoxypropoxy; examples of **(1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy** include 2-(methoxymethoxy)ethoxy,

2-(2-methoxyethoxy)ethoxy; 3-(2-methoxyethoxy)propoxy and 2-(2-ethoxyethoxy)ethoxy; examples of **(1-4C)alkylS(O)$_2$amino** include methylsulfonylamino and ethylsulfonylamino; examples of **(1-4C)alkanoylamino** and **(1-6C)alkanoylamino** include formamido, acetamido and propionylamino; examples of **(1-4C)alkoxycarbonylamino** include methoxycarbonylamino and ethoxycarbonylamino; examples of **N-(1-4C)alkyl-N-(1-6C)alkanoylamino** include N-methylacetamido, N-ethylacetamido and N-methylpropionamido; examples of **(1-4C)alkylS(O)$_p$NH-** wherein p is 1 or 2 include methylsulfinylamino, methylsulfonylamino, ethylsulfinylamino and ethylsulfonylamino; examples of **(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-** wherein p is 1 or 2 include methylsulfinylmethylamino, methylsulfonylmethylamino, 2-(ethylsulfinyl)ethylamino and 2-(ethylsulfonyl)ethylamino; examples of **fluoro(1-4C)alkylS(O)$_p$NH-** wherein p is 1 or 2 include trifluoromethylsulfinylamino and trifluoromethylsulfonylamino; examples of **fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)NH-** wherein p is 1 or 2 include trifluoromethylsulfinylmethylamino and trifluoromethylsulfonylmethylamino examples of **(1-4C)alkoxy(hydroxy)phosphoryl** include methoxy(hydroxy)phosphoryl and ethoxy(hydroxy)phosphoryl; examples of **di-(1-4C)alkoxyphosphoryl** include di-methoxyphosphoryl, di-ethoxyphosphoryl and ethoxy(methoxy)phosphoryl; examples of **(1-4C)alkylS(O)$_q$-** wherein q is 0, 1 or 2 include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of **phenylS(O)$_q$** and **naphthylS(O)$_q$-** wherein q is 0, 1 or 2 are phenylthio, phenylsulfinyl, phenylsulfonyl and naphthylthio, naphthylsulfinyl and naphthylsulfonyl respectively; examples of **benzyloxy-(1-4C)alkyl** include benzyloxymethyl and benzyloxyethyl; examples of a **(3-4C)alkylene** chain are trimethylene or tetramethylene; examples of **(1-6C)alkoxy-(1-6C)alkyl** include methoxymethyl, ethoxymethyl and 2-methoxyethyl; examples of **hydroxy-(2-6C)alkoxy** include 2-hydroxyethoxy and 3-hydroxypropoxy; examples of **(1-4C)alkylamino-(2-6C)alkoxy** include 2-methylaminoethoxy and 2-ethylaminoethoxy; examples of **di-(1-4C)alkylamino-(2-6C)alkoxy** include 2-dimethylaminoethoxy and 2-diethylaminoethoxy; examples of **phenyl(1-4C)alkyl** include benzyl and phenethyl; examples of **(1-4C)alkylcarbamoyl** include methylcarbamoyl and ethylcarbamoyl; examples of **di((1-4C)alkyl)carbamoyl** include di(methyl)carbamoyl and di(ethyl)carbamoyl; examples of **hydroxyimino(1-4C)alkyl** include hydroxyiminomethyl, 2-(hydroxyimino)ethyl and 1-

(hydroxyimino)ethyl; examples of **(1-4C)alkoxyimino-(1-4C)alkyl** include methoxyiminomethyl, ethoxyiminomethyl, 1-(methoxyimino)ethyl and 2-(methoxyimino)ethyl; examples of **halo(1-4C)alkyl** include, halomethyl, 1-haloethyl, 2-haloethyl, and 3-halopropyl; examples of **nitro(1-4C)alkyl** include nitromethyl, 1-nitroethyl, 2-nitroethyl and 3-nitropropyl; examples of **amino(1-4C)alkyl** include aminomethyl, 1-aminoethyl, 2-aminoethyl and 3-aminopropyl; examples of **cyano(1-4C)alkyl** include cyanomethyl, 1-cyanoethyl, 2-cyanoethyl and 3-cyanopropyl; examples of **(1-4C)alkanesulfonamido** include methanesulfonamido and ethanesulfonamido; examples of **(1-4C)alkylaminosulfonyl** include methylaminosulfonyl and ethylaminosulfonyl; and examples of **di-(1-4C)alkylaminosulfonyl** include dimethylaminosulfonyl, diethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl; examples of **(1-4C)alkanesulfonyloxy** include methylsulfonyloxy, ethylsulfonyloxy and propylsulfonyloxy; examples of **(1-4C)alkanoyloxy** include acetoxy; examples of **(1-4C)alkylaminocarbonyl** include methylaminocarbonyl and ethylaminocarbonyl; examples of **di((1-4C)alkyl)aminocarbonyl** include dimethylaminocarbonyl and diethylaminocarbonyl; examples of **(3-8C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **(4-7C)cycloalkyl** include cyclobutyl, cyclopentyl and cyclohexyl; examples of **di(N-(1-4C)alkyl)aminomethylimino** include dimethylaminomethylimino and diethylaminomethylimino.

Particular values for AR2 include, for example, for those AR2 containing one heteroatom, furan, pyrrole, thiophene; for those AR2 containing one to four N atoms, pyrazole, imidazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3- & 1,2,4-triazole and tetrazole; for those AR2 containing one N and one O atom, oxazole, isoxazole and oxazine; for those AR2 containing one N and one S atom, thiazole and isothiazole; for those AR2 containing two N atoms and one S atom, 1,2,4- and 1,3,4-thiadiazole.

Particular examples of AR2a include, for example, dihydropyrrole (especially 2,5-dihydropyrrol-4-yl) and tetrahydropyridine (especially 1,2,5,6-tetrahydropyrid-4-yl).

Particular examples of AR2b include, for example, tetrahydrofuran, pyrrolidine, morpholine (preferably morpholino), thiomorpholine (preferably thiomorpholino), piperazine (preferably piperazino), imidazoline and piperidine, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl.

Particular values for AR3 include, for example, bicyclic benzo-fused systems containing a 5- or 6-membered heteroaryl ring containing one nitrogen atom and optionally 1-3 further heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, indole, benzofuran, benzothiophene, benzimidazole, benzothiazole, benzisothiazole, benzoxazole, benzisoxazole, quinoline, quinoxaline, quinazoline, phthalazine and cinnoline.

Other particular examples of AR3 include 5/5-, 5/6 and 6/6 bicyclic ring systems containing heteroatoms in both of the rings. Specific examples of such ring systems include, for example, purine and naphthyridine.

Further particular examples of AR3 include bicyclic heteroaryl ring systems with at least one bridgehead nitrogen and optionally a further 1-3 heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, 3H-pyrrolo[1,2-a]pyrrole, pyrrolo[2,1-b]thiazole, 1H-imidazo[1,2-a]pyrrole, 1H-imidazo[1,2-a]imidazole, 1H,3H-pyrrolo[1,2-c]oxazole, 1H-imidazo[1,5-a]pyrrole, pyrrolo[1,2-b]isoxazole, imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, indolizine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrazine, pyrrolo[1,2-a]pyrimidine, pyrido[2,1-c]-s-triazole, s-triazole[1,5-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, imidazo[1,5-a]pyrazine, imidazo[1,5-a]pyrimidine, imidazo[1,2-b]-pyridazine, s-triazolo[4,3-a]pyrimidine, imidazo[5,1-b]oxazole and imidazo[2,1-b]oxazole. Other specific examples of such ring systems include, for example, [1H]-pyrrolo[2,1-c]oxazine, [3H]-oxazolo[3,4-a]pyridine, [6H]-pyrrolo[2,1-c]oxazine and pyrido[2,1-c][1,4]oxazine. Other specific examples of 5/5- bicyclic ring systems are imidazooxazole or imidazothiazole, in particular imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, imidazo[5,1-b]oxazole or imidazo[2,1-b]oxazole.

Particular examples of AR3a and AR3b include, for example, indoline, 1,3,4,6,9,9a-hexahydropyrido[2,1c][1,4]oxazin-8-yl, 1,2,3,5,8,8a-hexahydroimidazo[1,5a]pyridin-7-yl, 1,5,8,8a-tetrahydrooxazolo[3,4a]pyridin-7-yl, 1,5,6,7,8,8a-hexahydrooxazolo[3,4a]pyridin-7-yl, (7aS)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, (7aS)[5H]-1,2,3,7a-tetrahydropyrrolo[1,2c]imidazol-6-yl,

(7aR)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, [3H,5H]-pyrrolo[1,2-c]oxazol-6-yl, [5H]-2,3-dihydropyrrolo[1,2-c]imidazol-6-yl, [3H,5H]-pyrrolo[1,2-c]thiazol-6-yl, [3H,5H]-1,7a-dihydropyrrolo[1,2-c]thiazol-6-yl, [5H]-pyrrolo[1,2-c]imidazol-6-yl, [1H]-3,4,8,8a-tetrahydropyrrolo[2,1-c]oxazin-7-yl, [3H]-1,5,8,8a-tetrahydrooxazolo[3,4-a]pyrid-7-yl, [3H]-5,8-dihydroxazolo[3,4-a]pyrid-7-yl and 5,8-dihydroimidazo[1,5-a]pyrid-7-yl.

Particular values for AR4 include, for example, pyrrolo[a]quinoline, 2,3-pyrroloisoquinoline, pyrrolo[a]isoquinoline, 1H-pyrrolo[1,2-a]benzimidazole, 9H-imidazo[1,2-a]indole, 5H-imidazo[2,1-a]isoindole, 1H-imidazo[3,4-a]indole, imidazo[1,2-a]quinoline, imidazo[2,1-a]isoquinoline, imidazo[1,5-a]quinoline and imidazo[5,1-a]isoquinoline.

The nomenclature used is that found in, for example, "Heterocyclic Compounds (Systems with bridgehead nitrogen), W.L.Mosby (Intercsience Publishers Inc., New York), 1961, Parts 1 and 2.

Where optional substituents are listed such substitution is preferably not geminal disubstitution unless stated otherwise. If not stated elsewhere suitable optional substituents for a particular group are those as stated for similar groups herein.

Suitable substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 are (on an available carbon atom) up to three substituents independently selected from (1-4C)alkyl {optionally substituted by (preferably one) substituents selected independently from hydroxy, trifluoromethyl, (1-4C)alkyl S(O)q- (q is 0, 1 or 2) (this last substituent preferably on AR1 only), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, cyano, nitro, (1-4C)alkanoylamino, -CONRvRw or -NRvRw}, trifluoromethyl, hydroxy, halo, nitro, cyano, thiol, (1-4C)alkoxy, (1-4C)alkanoyloxy, dimethylaminomethyleneaminocarbonyl, di(N-(1-4C)alkyl)aminomethylimino, carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, (1-4C)alkylSO$_2$amino, (2-4C)alkenyl {optionally substituted by carboxy or (1-4C)alkoxycarbonyl}, (2-4C)alkynyl, (1-4C)alkanoylamino, oxo (=O), thioxo (=S), (1-4C)alkanoylamino {the (1-4C)alkanoyl group being optionally substituted by hydroxy}, (1-4C)alkyl S(O)q- (q is 0, 1 or 2) {the (1-4C)alkyl group being optionally substituted by one or more groups independently selected from cyano, hydroxy and (1-4C)alkoxy}, -CONRvRw or -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl].

Further suitable substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 (on an available carbon atom), and also on alkyl groups (unless indicated otherwise) are up to three substituents independently selected from trifluoromethoxy, benzoylamino, benzoyl, phenyl {optionally substituted by up to three substituents independently selected from halo, (1-4C)alkoxy or cyano}, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, thiophene, hydroxyimino(1-4C)alkyl, (1-4C)alkoxyimino(1-4C)alkyl, halo-(1-4C)alkyl, (1-4C)alkanesulfonamido, $-SO_2NRvRw$ [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl].

Preferable optional substituents on Ar2b as 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl or 1,4-dioxan-2-yl are mono- or disubstitution by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano, trifluoromethyl and phenyl].

Preferable optional substituents on CY1 & CY2 are mono- or disubstitution by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano, and trifluoromethyl.

Suitable substituents on AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4 and AR4a are (on an available nitrogen atom, where such substitution does not result in quaternization) (1-4C)alkyl, (1-4C)alkanoyl {wherein the (1-4C)alkyl and (1-4C)alkanoyl groups are optionally substituted by (preferably one) substituents independently selected from cyano, hydroxy, nitro, trifluoromethyl, (1-4C)alkyl S(O)q- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONRvRw or -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]}, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxycarbonyl or oxo (to form an N-oxide).

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine,

N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

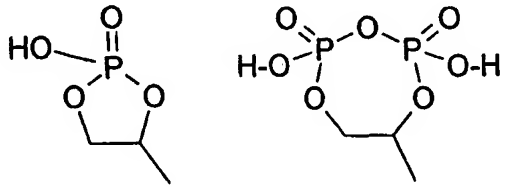
e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-onylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for

example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An in-vivo hydrolysable ester of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof containing a hydroxy group or groups includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include chloromethyl or aminomethyl, (1-4C)alkylaminomethyl and di-((1-4C)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4-position of the benzoyl ring.

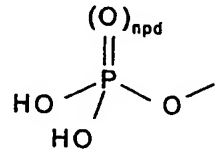
Certain suitable in-vivo hydrolysable esters of a compound of the formula (I) are described within the definitions listed in this specification, for example esters described by the definition (Rc2d), and some groups within (Rc2c). Suitable in-vivo hydrolysable esters of a compound of the formula (I) are described as follows. For example, a 1,2-diol may be cyclised to form a cyclic ester of formula (PD1) or a pyrophosphate of formula (PD2) :



(PD1) **(PD2)**

Particularly interesting are such cyclised pro-drugs when the 1,2-diol is on a (1-4C)alkyl chain linked to a carbonyl group in a substituent of formula Rc borne by a nitrogen atom in (TC4). Esters of compounds of formula (I) wherein the HO- function/s in (PD1) and (PD2) are protected by (1-4C)alkyl, phenyl or benzyl are useful intermediates for the preparation of such pro-drugs.

Further in-vivo hydrolysable esters include phosphoramidic esters, and also compounds of formula (I) in which any free hydroxy group independently forms a phosphoryl (npd is 1) or phosphiryl (npd is 0) ester of the formula (PD3) :



(PD3)

Useful intermediates for the preparation of such esters include compounds containing a group/s of formula (PD3) in which either or both of the -OH groups in (PD3) is independently protected by (1-4C)alkyl (such compounds also being interesting compounds in their own right), phenyl or phenyl-(1-4C)alkyl (such phenyl groups being optionally substituted by 1 or 2 groups independently selected from (1-4C)alkyl, nitro, halo and (1-4C)alkoxy).

Thus, prodrugs containing groups such as (PD1), (PD2) and (PD3) may be prepared by reaction of a compound of formula (I) containing suitable hydroxy group/s with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection.

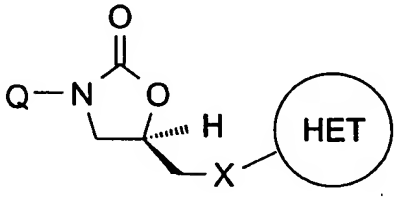
When a compound of formula (I) contains a number of free hydroxy group, those groups not being converted into a prodrug functionality may be protected (for example, using a t-butyl-dimethylsilyl group), and later deprotected. Also, enzymatic methods may be used to selectively phosphorylate or dephosphorylate alcohol functionalities.

Other interesting in-vivo hydrolysable esters include, for example, those in which Rc is defined by, for example, $R^{14}C(O)O(1\text{-}6C)alkyl\text{-}CO\text{-}$ (wherein R^{14} is for example, benzyloxy-(1-4C)alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(1-4C)piperazino-(1-4C)alkyl, piperazino-(1-4C)alkyl and morpholino-(1-4C)alkyl.

Where pharmaceutically-acceptable salts of an in-vivo hydrolysable ester may be formed this is achieved by conventional techniques. Thus, for example, compounds containing a group of formula (PD1), (PD2) and/or (PD3) may ionise (partially or fully) to form salts with an appropriate number of counter-ions. Thus, by way of example, if an in-vivo

hydrolysable ester prodrug of a compound of formula (I) contains two (PD3) groups, there are four HO-P- functionalities present in the overall molecule, each of which may form an appropriate salt (i.e. the overall molecule may form, for example, a mono-, di-, tri- or tetra-sodium salt).

The compounds of the present invention have a chiral centre at the C-5 position of the oxazolidinone ring. The pharmaceutically active enantiomer is of the formula (IA):



(IA)

The present invention includes the pure enantiomer depicted above or mixtures of the 5R and 5S enantiomers, for example a racemic mixture. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. For the avoidance of doubt the enantiomer depicted above is the 5R enantiomer.

Furthermore, some compounds of the formula (I) may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereo-isomers, and racemic mixtures, that possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by biotransformation or by chromatographic separation) and how to determine antibacterial activity as described hereinafter.

The invention relates to all tautomeric forms of the compounds of the formula (I) that possess antibacterial activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial activity.

It is also to be understood that certain compounds of the formula (I) may exhibit polymorphism, and that the invention encompasses all such forms which possess antibacterial

activity.

As stated before, we have discovered a range of compounds that have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics. Physical and/or pharmacokinetic properties, for example increased stability to mammalian peptidase metabolism and a favourable toxicological profile are important features. The following compounds possess particularly favourable physical and/or pharmacokinetic properties and are preferred.

Particularly preferred compounds of the invention comprise a compound of formula (I) or of formula (IP), or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein the substituents Q, X, HET, T and other substituents mentioned above have values disclosed hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter):

Preferably Q is selected from Q1, Q2, Q4, Q6 and Q9; especially Q1, Q2 and Q9; more particularly Q1 and Q2; and most preferably Q is Q1.

Preferably T is selected from (TAf), (TDb) or (TC); especially groups (TCb) and (TCc); more particularly (TC2), (TC3) and (TC4); and most preferably (TC5), (TC7) or (TC9), and most particularly (TC5). Especially preferred is each of these values of T when present in Q1 and Q2, particularly in Q1.

Preferable values for other substituents (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter) are :-

(a) Preferably X is -O-;

(a1) In another aspect X is -S-;

(a2) In another embodiment X can also be -SO- or $-SO_2-$;

(b) Preferably HET is pyridine, pyridazine or pyrazine; more preferably HET is pyridin-2-yl, pyridazin-3-yl or pyrazin-2-yl;

(b1) Preferably HET is unsubstituted;

(c) Preferably Rp is hydrogen;

(d) Preferably Rp1 and Rp2 are independently selected from hydrogen, (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl;

(e) Most preferably Rp1 and Rp2 are hydrogen;

(f) Preferably one of R^2 and R^3 is hydrogen and the other fluoro;

(g) In another aspect both R^2 and R^3 are fluoro;

(h) Preferably >A-B- is of the formula >C=CH- (i.e. Rr is preferably hydrogen) or >N-CH_2-;

(i) Preferably D is -O- or >NRcp;

(j) Preferably Rcp is AR, $R^{13p}CO$-, $R^{13p}SO_2$-, $R^{13p}CS$-;

(k) More preferably Rcp is AR (most preferably benzyl, pyrimidyl, pyridinyl, pyridazinyl or pyrazinyl) or $R^{13p}CO$- (especially $R^{13p}CO$-);

(l) Preferably AR is 5- or 6-membered heteroaryl; more preferably AR is 6-membered heteroaryl, such as pyridinyl;

(m) Preferred substituents for phenyl and carbon atoms in heteroaryl (mono- and bicyclic) ring systems in AR, R^{14p} and Ri include halo, (1-4C)alkyl, hydroxy, nitro, amino, cyano, (1-4C)alkylS(O)$_p$- and (1-4C)alkoxy;

(n) Preferably the optionally substituted ring systems in AR, R^{14p} and Ri are unsubstituted;

(n1) In another embodiment in the definition of R^{13p} in (PC) of embodiment (IP), 1,3-dioxolan-4-yl and 1,4-dioxan-2-yl are excluded.

(o) Preferably R^{13p} is (1-4C)alkoxycarbonyl, hydroxy(1-4C)alkyl, (1-4C)alkyl (optionally substituted by one or two hydroxy groups, or by an (1-4C)alkanoyl group), (1-4C)alkylamino, dimethylamino(1-4C)alkyl, (1-4C)alkoxymethyl, (1-4C)alkanoylmethyl, (1-4C)alkanoyloxy(1-4C)alkyl, (1-5C)alkoxy or 2-cyanoethyl;

(p) More preferably R^{13p} is 1,2-dihydroxyethyl, 1,3-dihydroxyprop-2-yl, 1,2,3-trihydroxyprop-1-yl, methoxycarbonyl, hydroxymethyl, methyl, methylamino, dimethylaminomethyl, methoxymethyl, acetoxymethyl, methoxy, methylthio, naphthyl, tert-butoxy or 2-cyanoethyl;

(p1) Yet more preferably R^{13p} is 1,2-dihydroxyethyl, 1,3-dihydroxyprop-2-yl or 1,2,3-trihydroxyprop-1-yl;

(q) Preferred optional substituents for (1-10C)alkyl in R^{14p} are hydroxy, cyano, amino, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-4C)alkylS(O)$_p$- (wherein p is 1 or 2), carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkoxy, piperazino or morpholino;

(r) Preferred optional substituents for (1-6C)alkyl in R^{15p} are hydroxy, (1-4C)alkoxy, cyano, amino, (1-4C)alkylamino, di((1-2C)alkyl)amino, (1-4C)alkylS(O)$_p$- (wherein p is 1 or

2);

(s) Preferably 5- or 6-membered heteroaryl in R^{14p} is pyridinyl or imidazol-1-yl;

(t) Preferably R^{15p} is (1-6C)alkyl; most preferably R^{15p} is tert-butyl or methyl;

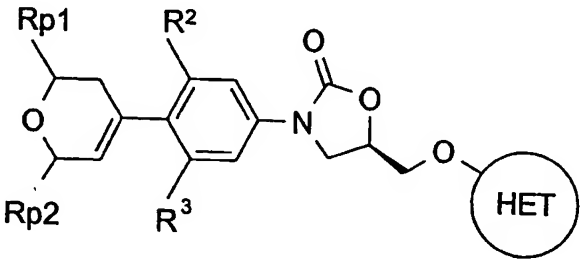
(u) Preferably R^{17p} is cyano or fluoro;

(v) Preferably R^{16p} is hydrogen;

(w) Preferably CY is naphthoxy, especially naphth-1-oxy or naphth-2-oxy.

Where preferable values are given for substituents in a compound of formula (IP), the corresponding substituents in a compound of formula (I) have the same preferable values (thus, for example, R^{13} and Rc in formula (I) correspond with Rcp and R^{13p} in formula (IP), and similarly for groups D and G). For compounds of formula (I) preferred values for Rc are those in group (Rc2). The preferred values for R^{13p} listed above for compounds of formula (IP) are also preferred values for R^{13} in compounds of formula (I). In the definition of (Rc2c) the AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups are preferably excluded.

Especially preferred compounds of the present invention are of the formula (IB):



(IB)

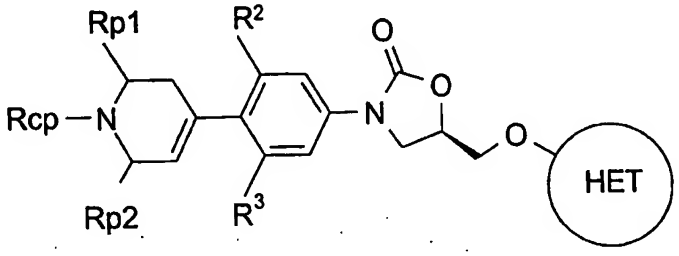
wherein HET is pyridin-2-yl or pyrazin-2-yl (especially pyridin-2-yl); R^2 and R^3 are independently hydrogen or fluoro; and Rp1 and Rp2 are independently hydrogen, hydroxy, bromo, (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl; or pharmaceutically-acceptable salts thereof.

Further especially preferred compounds of the invention are of the formula (IB) wherein HET is pyridin-2-yl or pyrazin-2-yl (especially pyridin-2-yl); R^2 and R^3 are independently hydrogen or fluoro; and Rp1 and Rp2 are independently hydrogen, AR-oxymethyl or AR-thiomethyl (wherein AR is phenyl, phenyl-(1-4C)alkyl, naphthyl, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole,

isothiazole, thiazole or thiophene); or pharmaceutically-acceptable salts thereof.

Of the above especially preferred compounds of the invention of the formula (IB), particularly preferred compounds are those wherein Rp1 and Rp2 are hydrogen are particularly preferred.

Further, especially preferred compounds of the invention are of the formula (IC):



(IC)

wherein HET is pyridin-2-yl or pyrazin-2-yl (especially pyridin-2-yl); R^2 and R^3 are independently hydrogen or fluoro; Rp1 and Rp2 are independently hydrogen, AR-oxymethyl or AR-thiomethyl (wherein AR is phenyl, phenyl-(1-4C)alkyl, naphthyl, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole or thiophene), (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl and Rcp is cyano, pyrimidin-2-yl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl or Rcp is of the formula $R^{13p}CO$-, $R^{13p}SO_2$- or $R^{13p}CS$- (wherein R^{13p} is hydrogen, (1-5C)alkyl [optionally substituted by one or more groups each independently selected from hydroxy and amino, or optionally monosubstituted by (1-4C)alkoxy, (1-4C)alkylS(O)$_q$-, (1-4C)alkylamino, (1-4C)alkanoyl, naphthoxy, (2-6C)alkanoylamino or (1-4C)alkylS(O)$_p$NH- wherein p is 1 or 2 and q is 0, 1 or 2], imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, pyridoimidazole, pyrimidoimidazole, quinoxaline, quinazoline, phthalazine, cinnoline or naphthyridine, or R^{13p} is of the formula $R^{14p}C(O)O$(1-6C)alkyl wherein R^{14p} is (1-6C)alkyl), or Rcp is of the formula RfC(=O)C(=O)- wherein Rf is (1-6C)alkoxy; or pharmaceutically-acceptable salts thereof.

Of the above especially preferred compounds of the invention of the formula (IC), those wherein HET is pyridin-2-yl or pyrazin-2-yl (especially pyridin-2-yl); R^2 and R^3 are independently hydrogen or fluoro; Rp1 and Rp2 are independently hydrogen, AR-oxymethyl or AR-thiomethyl (wherein AR is phenyl, phenyl-(1-4C)alkyl, naphthyl, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole,

thiazole or thiophene), (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl and Rcp is cyano, pyrimidin-2-yl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl or Rcp is of the formula $R^{13p}CO$-, $R^{13p}SO_2$- or $R^{13p}CS$- (wherein R^{13p} is hydrogen, (1-5C)alkyl [optionally substituted by one or more groups each independently selected from hydroxy and amino, or optionally monosubstituted by (1-4C)alkoxy, (1-4C)alkylS(O)q , (1-4C)alkylamino, (1-4C)alkanoyl, (2-6C)alkanoylamino or (1-4C)alkylS(O)$_p$NH- wherein p is 1 or 2 and q is 0, 1 or 2], pyridine, or R^{13p} is of the formula $R^{14p}C(O)O$(1-6C)alkyl wherein R^{14p} is (1-6C)alkyl), or Rcp is of the formula RfC(=O)C(=O)- wherein Rf is (1-6C)alkoxy; or pharmaceutically-acceptable salts thereof are further preferred.

Of the above especially preferred compounds of the invention of the formula (IC), particularly preferred compounds are those wherein HET is pyridin-2-yl or pyrazin-2-yl (especially pyridin-2-yl); R^2 and R^3 are independently hydrogen or fluoro; Rp1 and Rp2 are hydrogen, and Rcp is pyridin-2-yl (optionally substituted with cyano) or Rcp is of the formula $R^{13p}CO$- (wherein R^{13p} is hydrogen, 1,3-dioxolan-4-yl (optionally disubstituted with (1-4C)alkyl) or (1-5C)alkyl [optionally substituted by one or more hydroxy groups] or R^{13p} is of the formula $R^{14p}C(O)O$(1-6C)alkyl wherein R^{14p} is (1-6C)alkyl)); or pharmaceutically-acceptable salts thereof.

Of the above especially preferred compounds of the invention of the formula (IC), particularly preferred compounds are those wherein Rcp is of the formula $R^{13p}CO$- (wherein R^{13p} is hydrogen, 1,3-dioxolan-4-yl (optionally disubstituted with (1-4C)alkyl) or (1-5C)alkyl [substituted by two hydroxy groups]; or pharmaceutically-acceptable salts thereof.

In another aspect of the invention there are provided preferred compounds of the formula (IP) wherein -X-HET is pyridin-2-yloxy or pyrazin-2-yloxy ; >A-B- is >N-CH_2- and D is NRcp wherein Rcp is a 6-membered heteroaryl ring containing 1, 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl, halo, trifluoromethyl, (1-4C)alkyl S(O)$_q$- (wherein q is 0, 1 or 2), (1-4C)alkylS(O)$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, (1-4C)alkoxy, cyano or nitro; or pharmaceutically-acceptable salts thereof.

Another aspect of the invention is as decrcibed in the paragraph immediately above, but with -X-HET as pyridazin-3-yloxy.

In both of the above two paragraphs Rcp is preferably a 6-membered heteroaryl ring containing 1 or 2 ring nitrogen atoms, and is preferably substituted by cyano.

In all of the above aspects and preferred compounds of formula (IB) or (IC), in-vivo hydrolysable esters are preferred, especially phosphoryl esters (as defined by formula (PD3) with npd as 1).

In all of the above definitions the preferred compounds are as shown in formula (IA), i.e. the pharmaceutically active (5(R)) enantiomer.

Particular compounds of the present invention include the following (and the individual isomers where a mixture of isomers is possible) :-

Particular compounds of the present invention include :-

5(R)-Pyrid-2-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-(6-Chloropyridazin-3-yloxymethyl)-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Pyrazin-2-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Pyrimidin-4-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Pyridazin-3-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Pyrid-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(4-Methylpyrid-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(3-Methylpyrid-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(6-Chloropyridazin-3-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Pyridazin-3-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Pyrimidin-4-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Pyrazin-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(5-Chloropyridin-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one; and pharmaceutically-acceptable salts thereof.

Of the above particular compounds, especially preferred are

5(R)-Pyrid-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Pyrazin-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one; and pharmaceutically-acceptable salts thereof.

Other preferred compounds are those described in the Examples, and the 3,5-difluorophenyl analogues of the 3-fluorophenyl compounds described in the Examples.

Process section :

In a further aspect the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof. It will be appreciated that during certain of the following processes certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Examples of the use of resins as a protecting group are illustrated in Examples 135 & 136 herein.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist. Information on the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the following Patent and Application Publications, the contents of the relevant process sections of which are hereby incorporated herein by reference :

WO99/02525; WO98/54161; WO97/37980; WO97/30981 (& US5,736,545); WO97/21708 (& US5,719,154); WO97/10223; WO97/09328; WO96/35691; WO96/23788; WO96/15130; WO96/13502; WO95/25106 (& US5,668,286); WO95/14684 (& US5,652,238); WO95/07271 (& US5,688,792); WO94/13649; WO94/01110; WO93/23384 (& US5,547,950 & US 5,700,799); WO93/09103 (& US5,565,571, US5,654,428, US5,654,435, US5,756,732 & US5,801,246); US5,231,188; US5,247,090; US5,523,403; WO97/27188; WO97/30995; WO97/31917; WO98/01447; WO98/01446; WO99/10342; WO99/10343; WO99/11642; European Patent Application Nos. 0,359,418 and 0,609,905; 0,693,491 A1 (& US5,698,574); 0,694,543 A1 (& AU 24985/95); 0,694,544 A1 (& CA 2,154,024); 0,697,412 A1 (& US5,529,998); 0,738,726 A1 (& AU 50735/96); 0,785,201 A1 (& AU 10123/97); German Patent Application Nos. DE 195 14 313 A1 (& US5,529,998); DE 196 01 264 A1 (& AU 10098/97); DE 196 01 265 A1 (& AU 10097/97); DE 196 04 223 A1 (& AU 12516/97); DE 196 49 095 A1 (& AU 12517/97).

The following Patent and Application Publications may also provide useful information and the contents of the relevant process sections are hereby incorporated herein by reference :

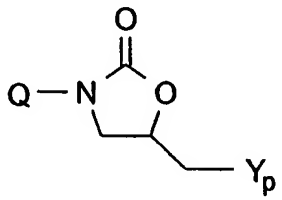
FR 2458547; FR 2500450(& GB 2094299, GB 2141716 & US 4,476,136); DE 2923295 (& GB 2028306, GB 2054575, US4,287,351, US4,348,393, US4,413,001, US4,435,415 & US4,526,786), DE 3017499 (& GB 2053196, US4,346,102 & US4,372,967); US4,705,799; European Patent Application Nos. 0,312,000; 0,127,902; 0,184,170; 0,352,781; 0,316,594;

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references to obtain necessary starting materials.

Thus, the present invention also provides that the compounds of the formulae (I) and pharmaceutically-acceptable salts and *in vivo* hydrolysable esters thereof, can be prepared by a process (a) to (g) as follows (wherein the variables are as defined above unless otherwise stated) :

(a) by modifying a substituent in or introducing a substituent into another compound of formula (I);

(b) by reaction of a compound of formula (II)



(II)

wherein Yp is hydroxy with a compound of the formula (b1) HET-OH or (b2) HET-Lg, wherein Lg is a suitable leaving group;

(c) by reaction of a compound of formula (II) wherein Yp is a leaving group, for example halogen, mesylate or tosylate, with a metal alkoxide compound of the formula HET-OM where M is an alkali metal, or another metal, such as silver, known to promote O-alkylation;

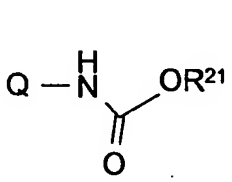
(d) by reaction of a compound of the formula Q-Zp wherein Zp is an isocyanate or amine group with an epoxide of the formula $CH_2(O)CH\text{-}CH_2O\text{-}HET$;

(e) when X is -S- by a process analogous to process (c) wherein (e1) a metal thioxide compound of the formula HET-SM where M is an alkali metal, or another metal, such as

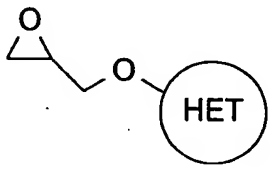
silver, known to promote S-alkylation; or (e2) alternatively by a process analogous to process (c) using HET-SH and a compound of formula (II) in which Yp is a suitable leaving group;

(f) when X is -SO- or -SO_2- by oxidation of a compound wherein X is -S-;

(g) by reaction of a urethane compound of formula (III) with a compound of formula (IV)



(III)



(IV)

wherein R^{21} is (1-6C)alkyl or benzyl; and thereafter if necessary :

(i) removing any protecting groups; (ii) forming a pharmaceutically-acceptable salt; (iii) forming an *in vivo* hydrolysable ester.

General guidance on reaction conditions and reagents may be obtained in Advanced Organic Chemistry, 4th Edition, Jerry March (publisher : J.Wiley & Sons), 1992. Necessary starting materials may be obtained by standard procedures of organic chemistry, such as described in this process section, in the Examples section or by analogous procedures within the ordinary skill of an organic chemist. Certain references are also provided (see above) which describe the preparation of certain suitable starting materials, for particular example see International Patent Application Publication No. WO 97/37980, the contents of which are incorporated here by reference. Processes analogous to those described in the references may also be used by the ordinary organic chemist to obtain necessary starting materials.

(a) Methods for converting substituents into other substituents are known in the art. For example an alkylthio group may be oxidised to an alkylsulfinyl or alkylsulfonyl group, a cyano group reduced to an amino group, a nitro group reduced to an amino group, a hydroxy group alkylated to a methoxy group, a hydroxy group thiomethylated to an arylthiomethyl or a heteroarylthiomethyl group (see, for example, Tet.Lett., 585, 1972), a carbonyl group converted to a thiocarbonyl group (eg. using Lawsson's reagent) or a bromo group converted to an alkylthio group. It is also possible to convert one Rc group into another Rc group as a final step in the preparation of a compound of the formula (I).

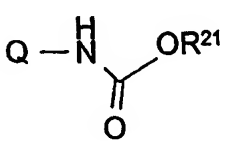
One compound of formula (I) may be converted into another compound of formula (I) by reacting a compound of formula (I) in which T is halo with a suitable compound to form another value of T. Thus, for example, T as halo may be displaced by suitable vinyl, aromatic, tropolone and nitrogen-linked systems as T by reaction using known Pd(0) coupling techniques.

Further examples of converting substituents into other substituents are contained in the accompanying non-limiting Examples.

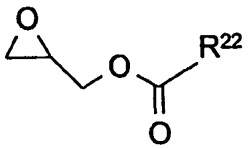
(b1) When HET-OH is used reaction (b1) is performed under Mitsunobu conditions, for example, in the presence of tri-n-butylphosphine and diethyl azodicarboxylate (DEAD) in an organic solvent such as THF, and in the temperature range 0°C - 60°C, but preferably at ambient temperature. Details of Mitsunobu reactions are contained in Tet. Letts., 31, 699, (1990); The Mitsunobu Reaction, D.L.Hughes, Organic Reactions, 1992, Vol.42, 335-656 and Progress in the Mitsunobu Reaction, D.L.Hughes, Organic Preparations and Procedures International, 1996, Vol.28, 127-164.

(b2) When HET-Lg is used reaction (b2) is performed using a suitably reactive HET and under basic conditions (using a base such as 1,8-diazabicyclo[5,4,0]undec-7-ene) which are sufficiently mild not to destroy the oxazolidinone ring structure. The skilled organic chemist will appreciate which suitable leaving group Lg (such as chloro or bromo) and reaction conditions to use.

Compounds of the formula (II) wherein Yp is hydroxy may be obtained by reacting a compound of the formula (III) with a compound of formula (V):



(III)



(V)

wherein R^{21} is (1-6C)alkyl or benzyl and R^{22} is (1-4C)alkyl or $-S(O)_q$(1-4C)alkyl where q is 0, 1 or 2. Preferably R^{22} is (1-4C)alkyl.

Compounds of the formula (II), (III) and (V) may be prepared by the skilled chemist, for example as described in International Patent Application Publication Nos. WO95/07271, WO97/27188, WO 97/30995, WO 98/01446 and WO 98/01446, the contents of which are hereby incorporated by reference, and by analogous processes.

If not commercially available, compounds of the formula HET-OH and HET-Lg may be prepared by procedures which are selected from standard chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the procedures described in the Examples. For example, standard chemical techniques are as described in Houben Weyl, Methoden der Organische Chemie.

(c) & (e) Reactions (c) and (e) are performed conveniently at a temperature in the range 25-60°C in a solvent such as NMP or DMF.

A compound of the formula (II) wherein Yp is fluoro may be prepared by reacting a compound of the formula (II) wherein Yp is hydroxy (hydroxy compound) with a fluorinating agent such as diethylaminosulfur trifluoride in an organic solvent such as dichloromethane in the temperature range of 0°C to ambient temperature.

When Yp is chloro, the compound of the formula (II) may be formed by reacting the hydroxy compound with a chlorinating agent. For example, by reacting the hydroxy compound with thionyl chloride, in a temperature range of ambient temperature to reflux, optionally in a chlorinated solvent such as dichloromethane or by reacting the hydroxy compound with carbon tetrachloride/triphenyl phosphine in dichloromethane, in a temperature range of 0°C to ambient temperature. A compound of the formula (II) wherein Yp is chloro or iodo may also be prepared from a compound of the formula (II) wherein Yp is mesylate or tosylate, by reacting the latter compound with lithium chloride or lithium iodide and crown ether, in a suitable organic solvent such as THF, in a temperature range of ambient temperature to reflux

When Yp is (1-4C)alkanesulfonyloxy or tosylate the compound (II) may be prepared by reacting the hydroxy compound with (1-4C)alkanesulfonyl chloride or tosyl chloride in the presence of a mild base such as triethylamine or pyridine.

Compounds of the formula HET-OM and HET-SM may be prepared by the skilled chemist from the corresponding HET-OH or HET-SH compound, using a suitable base, such as sodium hydride, silver carbonate, sodium carbonate or an alkoxide.

When X is -S- and a process is used that is analogous to process (c) but using HET-SH and a compound of formula (II) in which Yp is a suitable leaving group, a suitable leaving group is, for example, mesylate and a suitable base for the reaction is a base such as 1,8-diazabicyclo[5,4,0]undec-7-ene (see for example, Example 153).

(d) Reaction (d) is performed under conditions analogous to those described in the following references which disclose how suitable and analogous starting materials may be obtained.

Compounds of the formula Q-Zp wherein Zp is an isocyanate may be prepared by the skilled chemist, for example by analogous processes to those described in Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165. Compounds of the formula Q-Zp wherein Zp is a urethane (see process (i)) may be prepared by the skilled chemist, for example by analogous processes to those described in International Patent Application Publication Nos. WO 97/30995 and WO 97/37980.

A similar reaction to reaction (d) may be performed in which Q-Zp wherein Zp is a amine group is reacted with the epoxide (optionally in the presence of an organic base), and the product is reacted with, for example, phosgene to form the oxazolidinone ring. Such reactions and the preparation of starting materials in within the skill of the ordinary chemist with reference to the above-cited documents disclosing analogous reactions and preparations.

Epoxides of the formula $CH_2(O)CH\text{-}CH_2O\text{-}HET$ may be prepared from the corresponding $CH_2{=}CH\text{-}CH_2\text{-}O\text{-}HET$ compound. Certain such epoxide and alkene intermediates are novel and are provided as a further feature of the invention. Asymmetric epoxidation may be used to give the desired optical isomer.

(f) When X is -SO- or $-SO_2-$ the oxidation of a compound wherein X is -S- may be achieved by oxidising with standard reagents known in the art for the oxidation of a thio group to a sulfinyl or sulfonyl group. For example, a thio group may be oxidised to a sulfinyl group with a peracid such as m-chloroperoxybenzoic acid and oxidising agents such as potassium permanganate can be used to convert a thio group to a sulfonyl group.

(g) A compound of formula (III) is reacted with a compound of formula (IV) using similar conditions to those for reaction of a compound of the formula (III) with a compound of formula (V) described above. If not commercially available, the preparation of suitable starting materials of formulae (III) and (IV) is as described above, or by using analogous processes.

The removal of any protecting groups, the formation of a pharmaceutically-acceptable salt and/or the formation of an *in vivo* hydrolysable ester are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these steps, for

example the preparation of in-vivo hydrolysable ester prodrugs has been provided in the section above on such esters, and in certain of the following non-limiting Examples.

When an optically active form of a compound of the formula (I) is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the formula (I) is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of a compound of the formula (I) of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the formula (I), an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, aerosols (or sprays), drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example, ß-lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 1mg and 1g of a compound of this invention, preferably between 100mg and 1g of a compound. Especially preferred is a tablet or capsule which contains between 50mg and 800mg of a compound of this invention, particularly in the range 100mg to 500mg.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection, for example an injection which contains between 0.1% w/v and 50% w/v (between 1mg/ml and 500mg/ml) of a compound of this invention.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 0.5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention, the

composition being administered 1 to 4 times per day. In another embodiment a daily dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention is administered. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient may receive a daily oral dose which may be approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

A pharmaceutical composition to be dosed intravenously may contain advantageously (for example to enhance stability) a suitable bactericide, antioxidant or reducing agent, or a suitable sequestering agent.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Antibacterial Activity :

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically-acceptable compounds of the present invention show activity against enterococci, pneumococci and methicillin resistant strains of S.aureus and coagulase negative staphylococci. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The (antibacterial) properties of the compounds of the invention may also be demonstrated and assessed in-vivo in conventional tests, for example by oral and/or intravenous dosing of a compound to a warm-blooded mammal using standard techniques.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot. Typically, compounds are active in the range 0.01 to 256 μg/ml.

Staphylococci were tested on agar, using an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood, an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms.

Organism		MIC (µg/ml) Example 6
Staphylococcus aureus:		
	Oxford	0.5
	Novb. Res	2.0
	MRQR	1.0
Coagulase Negative Staphylococci		
	MS	0.5
	MR	1.0
Streptococcus pyogenes		
	C203	2.0
Enterococcus faecalis		2.0
Bacillus subtilis		0.5

Novb. Res = Novobiocin resistant

MRQR = methicillin resistant quinolone resistant

MR = methicillin resistant

MS = methicillin sensitive

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26°C and in air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the formula (I) were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were generally determined in DMSO-D6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, m, multiplet; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected];

(vi) intermediates were not generally fully characterised and purity was in general assessed by thin layer chromatographic, infra-red (IR), mass spectral (MS) or NMR analysis; and

(vii) in which the following abbreviations may be used :-

® is a Trademark; DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is mass spectroscopy; ESP is electrospray; THF is tetrahydrofuran; TFA is trifluoroacetic acid; NMP is N-methylpyrrolidone; HOBT is 1-hydroxy-benzotriazole; EtOAc is ethyl acetate; MeOH is methanol; phosphoryl is $(HO)_2$-P(O)-O-; phosphiryl is $(HO)_2$-P-O-; EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (hydrochloride); PTSA is para-toluenesulfonic acid.

Reference Example 1: 5(R)-Hydroxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one

5(R)-Hydroxymethyl-3-(3-fluoro-4-(4-*t*-butoxycarbonylpiperazin-1-yl)phenyl)-oxazolidin-2-one (International Patent Application Publication WO 93/23384, 43.1 g, 0.11 M) was suspended by stirring in ethanol (1000 ml) under nitrogen. An ethanol solution of hydrogen chloride (3.8 M, 400 ml) was added slowly, and the mixture was stirred at ambient temperature for 18 hours. The resulting precipitate was filtered, washed with diethyl ether (3 x 250 ml), and dried, to give 5(R)-hydroxymethyl-3-(3-fluoro-4-(piperazin-1-yl)phenyl)oxazolidin-2-one hydrochloride. A further crop was obtained by evaporation of the mother liquors to give a total yield of 38.7 g. ^{1}H-NMR (300MHz, DMSO-D6) δ: 3.17 (m, 8H); 3.53 (dd, 1H); 3.64 (dd, 1H); 3.79 (dd, 1H); 4.03 (t, 1H); 4.66 (m, 1H); 7.10 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H); 9.39 (br s, 2H). MS (ESP): 296 (MH^+) for $C_{14}H_{18}FN_3O_3$

5(R)-Hydroxymethyl-3-(3-fluoro-4-(piperazin-1-yl)phenyl)oxazolidin-2-one hydrochloride (25 g, 75.4 mM) was suspended by stirring in acetonitrile (700 ml) under nitrogen, and triethylamine (16.8 g, 166 mM) added. The mixture was stirred for 10 minutes and then 2-chloro-5-cyanopyridine (10.3 g, 75.4 mmol) added, and the mixture heated under reflux for 18 hours. After cooling, the resultant solid was filtered, washed with water (3 x 500 ml) and diethyl ether (2 x 500 ml) to give 5(R)-hydroxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)-oxazolidin-2-one. A further crop was obtained by evaporation of the mother liquors to give a total yield of 23.2 g. MS (ESP): 398 (MH^+) for $C_{20}H_{20}FN_5O_3$ ^{1}H-NMR (300MHz, DMSO-D6) δ: 3.03 (t, 4H); 3.54 (m, 1H); 3.63(m, 1H); 3.78 (t overlapping m, 5H); 4.03 (t, 1H); 4.66 (m, 1H); 5.18 (t, 1H); 6.97 (d, 1H); 7.07 (t, 1H); 7.20 (dd, 1H); 7.53 (dd, 1H); 7.85 (dd, 1H); 8.49 (d, 1H).

Example 1: 5(R)-Pyrid-2-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one

5(R)-Hydroxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)-oxazolidin-2-one (397 mg, 1 mM), 2-hydroxypyridine (104 mg, 1.1 mM) and polymer bound triphenylphosphine (3 mM/g, 416 mg, 1.25 mM), were suspended with stirring

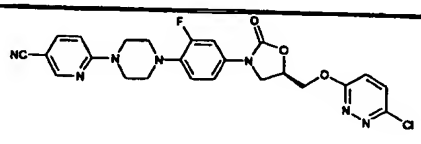
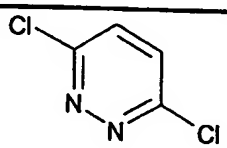
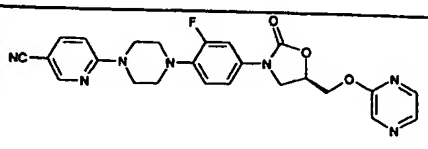
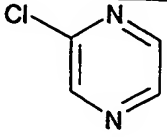
in dry tetrahydrofuran (10 ml). Di*iso*propylazodicarboxylate (242 mg, 1.2 mM) was added dropwise by syringe, and the mixture stirred at ambient temperature for 1 hour. The reaction mixture was filtered, evaporated to dryness, dissolved in ethyl acetate, and applied to a 10 g silica Mega Bond Elut® column, eluting with a mixture of ethyl acetate and *iso*hexane (1:1). Relevant fractions were combined and evaporated to give the title compound (45 mg). MS (ESP): 475 (MH^+) for $C_{25}H_{23}FN_6O_3$

^{1}H-NMR (300MHz,DMSO-D6) δ: 3.03 (t, 4H); 3.81 (t, 4H); 3.89 (dd, 1H); 4.17 (t, 1H); 4.47 (dd, 1H); 4.55 (dd, 1H); 5.03 (m, 1H); 6.82 (d, 1H); 6.99 (t overlapping dd, 2H); 7.08 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H); 7.70 (td, 1H); 7.85 (dd, 1H); 8.15 (dd, 1H); 8.48 (d, 1H).

Example 2 : 5(R)-(6-Chloropyridazin-3-yloxymethyl)-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

Example 3 : 5(R)-Pyrazin-2-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one

5(R)-Hydroxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)-oxazolidin-2-one (240 mg, 0.6 mM), was added in portions to a stirred suspension of sodium hydride (60% in oil, 26 mg, 0.65 mM) in dry *N,N*-dimethylformamide under nitrogen. The mixture was stirred at ambient temperature for 25 minutes, the appropriate chloroheterocycle (0.6 mM) added, and stirring continued for 18 hours. The mixture was diluted with water (20 ml), and the resulting precipitate filtered, washed with diethyl ether, and dried to give the title compounds.

Example	Product	Chloro-heterocycle	Yield (mg)	Notes
2			186	1
3			238	2

Notes 1:

^{1}H-NMR (300MHz,DMSO)- δ: 3.03 (t, 4H); 3.79 (t, 4H); 3.92 (dd, 1H); 4.18 (t, 1H); 4.65 (dd, 1H); 4.72 (dd, 1H); 5.09 (m, 1H); 6.97 (d, 1H); 7.08 (t, 1H); 7.21 (dd, 1H); 7.38 (d, 1H); 7.52 (dd, 1H); 7.80 (d, 1H); 7.86 (dd, 1H); 8.48 (d, 1H). MS: ESP+ (M+H) = 510 for $C_{24}H_{21}ClFN_7O_3$.

Notes 2 :

^{1}H-NMR (300MHz,DMSO): δ: 3.03 (t, 4H); 3.79 (t, 4H); 3.91 (dd, 1H); 4.18 (t, 1H); 4.53 (dd, 1H); 4.60 (dd, 1H); 5.08 (m, 1H); 6.98 (d, 1H); 7.08 (t, 1H); 7.22 (dd, 1H); 7.52 (dd, 1H); 7.86 (dd, 1H); 8.23 (overlapping m, 2H); 8.34 (s, 1H); 8.50 (d, 1H). MS: ESP+ (M+H) = 476 for $C_{24}H_{22}FN_7O_3$.

Example 4 : 5(R)-Pyrimidin-4-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one

5(R)-Hydroxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)-oxazolidin-2-one (397 mg, 1 mM), 4-hydroxypyrimidine (106 mg, 1.1 mM) and triphenylphosphine (327 mg, 1.25 mM), were suspended with stirring in dry tetrahydrofuran (10 ml). Di*iso*propylazodicarboxylate (242 mg, 1.2 mM) was added dropwise by syringe, and the mixture stirred at ambient temperature for 30 minutes. The reaction mixture was evaporated to dryness, dissolved in ethyl acetate / *iso*hexane (3:1), and applied to a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 3:1 ethyl acetate in *iso*hexane to pure ethyl acetate. Relevant fractions were combined and evaporated to give the title compound (240 mg). MS (ESP): 476 (MH^+) for $C_{24}H_{22}FN_7O_3$.

^{1}H-NMR (300MHz,DMSO): δ: 3.03 (t, 4H); 3.79 (t, 4H); 3.89 (dd, 1H); 4.17 (t, 1H); 4.56 (dd, 1H); 4.61 (dd, 1H); 5.06 (m, 1H); 6.96 (overlapping m, 2H); 7.08 (t, 1H); 7.20 (dd, 1H); 7.51 (dd, 1H); 7.86 (dd, 1H); 8.50 (d, 1H); 8.50 (d, 1H); 8.79 (s, 1H).

Example 5 : 5(R)-Pyridazin-3-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one

5(R)-(6-Chloropyridazin-3-yloxymethyl)-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (176 mg, 0.35 mM) was dissolved in *N,N*-dimethylformamide (20 ml) and triethylamine (71 mg, 0.7 mM) and palladium on charcoal (5%, 30 mg) added with stirring. The atmosphere in the vessel was replaced with hydrogen under a balloon, and the mixture stirred 18 hours at ambient temperature. Catalyst was filtered off through celite, solvent evaporated, and the residue dissolved in dichloromethane, and applied to a 20 g silica Mega Bond Elut column, eluting with a gradient increasing in polarity from pure dichloromethane to 19:1 dichloromethane in methanol. Relevant fractions were combined and evaporated to give the title compound (22 mg). MS (ES): 476 (MH^+) for $C_{24}H_{22}FN_7O_3$ NMR (DMSO-D6) δ: 3.04 (t, 4H); 3.81 (t, 4H); 3.94 (dd, 1H); 4.19 (t, 1H); 4.70 (overlapping m, 2H); 5.11 (m, 1H); 6.99 (d, 1H); 7.09 (t, 1H); 7.23 (overlapping m, 2H); 7.53 (dd, 1H); 7.61 (m, 1H); 7.86 (dd, 1H); 8.50 (d, 1H); 8.91 (dd, 1H).

Example 6: 5(R)-Pyrid-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

2-Hydroxypyridine (108mg, 1.14mmol) was added portionwise, at ambient temperature, to a stirred suspension of sodium hydride (48mg, 1.2mmol of a 60% dispersion in oil) in DMF (5ml) under an atmosphere of nitrogen. The mixture was stirred for 30 minutes then 5(R)-methylsulphonyloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one (International Patent Application Publication WO97/09328, 400mg, 1.08mmol) was added in one go. The reaction was stirred and heated at 60°C for 5 hours, then quenched in water and extracted with ethyl acetate. The extract was washed twice with water and once with saturated brine, dried over magnesium sulphate and evaporated to give an oil. The oil was purified by flash chromatography (Merck 9385 silica, 2.5% methanol / dichloromethane eluant) to give the title product (60mg, 15%) as a crystalline solid. MS: ESP^+ $(M+H)^+$= 371.

^{1}H-NMR (300MHz, $CDCl_3$): d = 2.50 (m, 2H), 3.94 (t, 2H), 3.98 (dd, 1H), 4.15 (t, 1H), 4.34 (m, 2H), 4.60 (d, 2H), 5.05 (m, 1H), 6.04 (m, 1H), 6.77 (d, 1H), 6.92 (dd, 1H), 7.26 (m, 2H), 7.42 (dd, 1H), 7.60 (m, 1H), 8.14 (dd, 1H).

Example 7: 5(R)-(4-Methylpyrid-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

Diisopropylazodicarboxylate (290mg, 1.43mmol) was added dropwise, at ambient temperature, to a stirred solution of 5(R)-hydroxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one (International Patent Application Publication WO 97/09328, 300mg, 1.02mmol), 2-hydroxy-4-methylpyridine (167mg, 1.53mmol) and triphenylphosphine (402mg, 1.53mmol) in THF (8ml). The resulting solution was stirred at ambient temperature for 30 minutes before evaporating the solvent to give an oil. The oil was purified by flash chromatography (Merck 9385 silica, ethyl acetate / isohexane(3:2) eluant) to give the title product (181mg, 46%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): d = 2.52 (m, 2H), 3.92 (t, 2H), 3.97 (dd, 1H), 4.12 (t, 1H), 4.32 (m, 2H), 4.59 (d, 2H), 5.02 (m, 1H), 6.06 (m, 1H), 6.59 (s, 1H), 6.75 (d, 1H), 7.26 (m, 2H), 7.41 (dd, 1H), 7.99 (d, 1H). MS: ESP^+ $(M+H)^+$= 385.

Example 8: 5(R)-(3-Methylpyrid-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

The title product was prepared by the general method of Example 2, using the same oxazolidinone starting material as Example 7 (300mg, 1.02mmol), sodium hydride (95mg, 2.37mmol of a 60% dispersion in oil) and 2-fluoro-3-methylpyridine (130mg, 1.17mmol) in DMF (3ml). The resultant reaction product was purified by flash chromatography (Merck 9385 silica, ethyl acetate / isohexane (7:3) eluant) to give the title product (50mg, 13%) as a crystalline solid. MS: ESP^+ $(M+H)^+$= 385.

^{1}H-NMR 9300MHz, $CDCl_3$): d = 2.12 (s, 3H), 2.51 (m, 2H), 3.92 (t, 2H), 3.99 (dd, 1H), 4.17 (t, 1H), 4.32 (m, 2H), 4.61 (m, 2H), 5.05 (m, 1H), 6.07 (m, 1H), 6.84 (dd, 1H), 7.27 (m, 2H), 7.35-7.44 (m, 2H), 7.06 (d, 1H).

Example 9: 5(R)-(6-Chloropyridazin-3-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

The title product was prepared by the general method of Example 8 using the same oxazolidinone starting material (600mg, 2.05mmol), sodium hydride (90mg, 2.25mmol of a 60% dispersion in oil) and 3,6-dichloropyridazine (350mg, 2.35mmol) in DMF (6ml). The mixture was stirred at ambient temperature for 18 hours then at 60°C for 6 hours, and the resultant product purified by flash chromatography (Merck 9385 silica, ethyl acetate / isohexane (7:3) eluant) to give the title product (178mg, 21%) as a crystalline solid. MS: ESP^+ $(M+H)^+$= 406/408.

^{1}H-NMR (300MHz, $CDCl_3$): d = 2.52 (m, 2H), 3.86-4.00 (m, 3H), 4.22 (m, 1H), 4.32 (m, 2H), 4.70-4.90 (m, 2H), 5.10 (m, 1H), 6.06 (m, 1H), 7.06 (dd, 2H), 7.18-7.33 (m, 2H), 7.44 (m, 2H).

Example 10: 5(R)-Pyridazin-3-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

30% Palladium on carbon (20mg) was added to a stirred suspension of Example 9 (240mg, 0.59mmol) and ammonium formate (112mg, 1.78mmol) in ethanol (10ml) under an atmosphere of nitrogen. The reaction was stirred at ambient temperature for 4 hours then filtered through celite. The filtrate was evaporated under reduced pressure to give a gum which was taken up in methanol (20ml) and stirred with sodium carbonate (500mg) for 30 minutes. The mixture was then filtered and the filtrate evaporated to give a gum, which was purified by flash chromatography (Merck 9385 silica, 3% methanol / dichloromethane eluant) to give the title product (91mg, 41%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): d = 2.52 (m, 2H), 3.92 (t, 2H), 3.97 (dd, 1H), 4.20 (t, 1H), 4.31 (m, 2H), 4.79 (dd, 1H), 4.88 (dd, 1H), 5.10 (m, 1H), 6.06 (m, 1H), 7.05 (d, 1H), 7.28 (m, 2H), 7.42 (m, 2H), 8.90 (d, 1H). MS: ESP^+ $(M+H)^+$= 372.

Example 11: 5(R)-Pyrimidin-4-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

The title product was prepared by the general method of Example 7, using the same oxazolidinone starting material (300mg, 1.02mmol), 4-hydroxypyrimidine (147mg,

1.53mmol), diisopropylazodicarboxylate (289mg, 1.43mmol) and triphenylphosphine (402mg, 1.53mmol) in THF (8ml). The resultant reaction product was purified by flash chromatography (Merck 9385 silica, 2.5% methanol / dichloromethane eluant) to give the title product (186mg, 49%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): d = 2.50 (m, 2H), 3.91-3.98 (m, 3H), 4.17 (t, 1H), 4.32 (m, 2H), 4.64 (dd, 1H), 4.72 (dd, 1H), 5.04 (m, 1H), 6.06 (m, 1H), 6.79 (d, 1H), 7.28 (m, 2H), 7.42 (dd, 1H), 8.49 (d, 1H), 8.78 (s, 1H). MS: ESP^+ $(M+H)^+$= 372.

Example 12: 5(R)-Pyrazin-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

The title product was prepared by the general method of Example 8 using the same oxazolidinone starting material (300mg, 1.02mmol), sodium hydride (45mg, 1.12mmol of a 60% dispersion in oil) and 2-chloropyrazine (130mg, 1.13mmol) in DMF (3ml). The resultant reaction product was purified by flash chromatography (Merck 9385 silica, 2.5% methanol / dichloromethane eluant) to give the title product (171mg, 45%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): d = 2.51 (m, 2H), 3.92 (t, 2H), 3.97 (dd, 1H), 4.08 (t, 1H), 4.32 (m, 2H), 4.62 (m, 2H), 5.08 (m, 1H), 6.06 (m, 1H), 7.28 (m, 2H), 7.43 (dd, 1H), 8.10 (t, 1H), 8.21 (d, 1H), 8.29 (d, 1H). MS: ESP^+ $(M+H)^+$= 372.

Example 13: 5(R)-(5-Chloropyridin-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

The title product was prepared by the general method of Example 7 using the same oxazolidinone starting material (300mg, 1.02mmol), 3-chloro-6-hydroxypyridine (146mg, 1.13mmol), diisopropylazodicarboxylate (227mg, 1.12mmol) and triphenylphosphine (305mg, 1.16mmol) in THF (5ml). The resultant reaction product was purified by flash chromatography (Merck 9385 silica, ethyl acetate / isohexane (3:2) eluant) to give the title product (197mg, 48%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): d = 2.51 (m, 2H), 3.90-4.00 (m, 3H), 4.14 (t, 1H), 4.30 (m, 2H), 4.56 (m, 2H), 5.02 (m, 1H), 6.05 (m, 1H), 6.74 (d, 1H), 7.20-7.30 (m, 2H), 7.40 (d, 1H), 7.55 (dd, 1H), 8.10 (d, 1H). MS: ESP^+ $(M+H)^+$= 405/407.

Example 14: 5(R)-Pyrid-2-yloxymethyl-3-(4-acetylphenyl)-oxazolidin-2-one

5(R)-Hydroxymethyl-3-(4-acetylphenyl)-oxazolidin-2-one (C.L.J.Wang et al, Tetrahedron, Vol.45, 1323, (1989); 300mg, 1.28mmol) was added portionwise, at room temperature, to a stirred suspension of sodium hydride (56mg, 1.4mmol of a 60% dispersion in oil) in DMF (3ml) under an atmosphere of nitrogen. The mixture was stirred for an additional 15 min. then 2-fluoropyridine (148mg, 1.53mmol) added. The reaction was stirred for 18 hr. before quenching in water and extracting with ethyl acetate. The extract was washed with water (3x) and saturated brine (1x) then evaporated to give an orange gum. Purified by flash chromatography (Merck 9385 silica, ethyl acetate / isohexane(7:3)) to give the title compound (27mg, 7%) as a colourless crystalline solid. MS: ESP^+ $(M+H)^+ = 313$.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.60 (s, 3H), 4.07 (dd, 1H), 4.22 (t, 1H), 4.62 (d, 2H), 5.08 (m, 1H), 6.77 (d, 1H), 6.93 (dd, 1H), 7.59 (m, 1H), 7.68 (d, 2H), 7.99 (d, 2H), 8.14 (d, 1H).

Example 15: 5(R)-Pyrid-2-yloxymethyl-3-(4-(4-bromoimidazol-1-yl)-3-fluorophenyl)-oxazolidin-2-one

Prepared by the general method of Example 7 using 5(R)-hydroxymethyl-3-(4-(4-bromoimidazol-1-yl)-3-fluoro)phenyl)-oxazolidin-2-one (WO97/31917; 300mg, 0.84mmol), 2-hydroxypyridine (96mg, 1.01 mmol), diisopropylazodicarboxylate (204mg, 1.012 mmol) and triphenylphosphine (270mg, 1.03mmol) in THF (5ml). Purified by flash chromatography (Merck 9385 silica, 2.5% methanol / dichloromethane) to give the title compound (156mg, 43%) as a colourless crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 4.06 (dd, 1H), 4.18 (t, 1H), 4.62 (d, 2H), 5.10 (m, 1H), 6.78 (d, 1H), 6.94 (m, 1H), 7.20 (d, 1H), 7.37 (m, 2H), 7.55-7.67 (m, 2H), 7.72 (d, 1H), 8.14 (d, 1H). MS: ESP^+ $(M+H)^+ = 433/435$.

Example 16: 5(R)-Pyrid-2-yloxymethyl-3-(4-methylthiophenyl)-oxazolidin-2-one

Prepared by the general method of Example 7 using 5(R)-hydroxymethyl-3-(4-methylthiophenyl)-oxazolidin-2-one (prepared from the reaction of 4-methylthioaniline and (R)-glycidyl butyrate), 200mg, 0.84mmol), 2-hydroxypyridine (90mg, 0.95mmol), diisopropylazodicarboxylate (190mg, 0.94mmol) and triphenylphosphine (252mg, 0.96mmol) in THF (5ml). Purified by flash chromatography (Merck 9385 silica, ethyl acetate / isohexane (3:2)) to give the title compound (123mg, 46%) as a colourless crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.49 (s, 3H), 3.97 (dd, 1H), 4.13 (t, 1H), 4.60 (d, 2H), 5.03 (m, 1H), 6.77 (d, 1H), 6.92 (dd, 1H), 7.30 (d, 2H), 7.51 (d, 2H), 7.58 (m, 1H), 8.13 (d, 1H). MS: ESP^+ $(M+H)^+$= 317.

Example 17: 5(R)-Pyrid-3-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

Prepared by the general method of Example 6 using the same starting material, (400mg, 1.08mmol), sodium hydride (48mg, 1.2mmol of a 60% dispersion) and 3-hydroxypyridine (108mg, 1.14mmol) in DMF (5ml). Purified by flash chromatography (Merck 9385 silica, 3% methanol / dichloromethane) to give the title compound (231mg, 58%) as a colourless solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.50 (m, 2H), 3.92 (t, 2H), 4.08 (dd, 1H), 4.21 (t, 1H), 4.26-4.34 (m, 4H), 5.03 (m, 1H), 6.06 (m, 1H), 7.20-7.34 (m, 4H), 7.44 (d, 1H), 8.30 (m, 1H), 8.34 (m, 1H). MS: ESP^+ $(M+H)^+$= 371.

There is no Example 18.

Example 19: 5(R)-(6-Methylpyrid-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

Prepared by the general method of Example 7 the same starting material (300mg, 1.02mmol), 2-hydroxy-6-methylpyridine (167mg, 1.53mmol), diisopropylazodicarboxylate (290mg, 1.43mmol) and triphenylphosphine (402mg,

1.53mmol) in THF (8ml). Purified by flash chromatography (Merck 9385 silica, 40% ethyl acetate / isohexane) to give the title compound (197mg, 50%) as a crystalline solid. MS: ESP^+ $(M+H)^+ = 385$.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.44 (s, 3H), 2.50 (m, 2H), 3.91 (t, 2H), 4.00 (dd, 1H), 4.12 (t, 1H), 4.31 (m, 2H), 4.52-4.67 (m, 2H), 5.03 (m, 1H), 6.05 (m, 1H), 6.54 (d, 2H), 6.74 (d, 2H), 7.21-7.32 (m, 2H), 7.42 (d, 1H), 7.48 (t, 1H).

Example 20: 5(R)-(Pyrid-4-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one

Prepared by the general method of Example 19 using the same starting material (300mg, 1.02mmol), 4 hydroxypyridine (107mg, 1.13mmol), diisopropylazodicarboxylate (227mg, 1.12mmol) and triphenylphosphine (305mg, 1.16mmol) in THF (5ml). Purified by flash chromatography (Merck 9385 silica, 5% methanol / dichloromethane) to give the title compound (150mg, 40%) as a crystalline solid.

^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.51 (m, 2H), 3.92 (t, 2H), 4.04 (dd, 1H), 4.21 (t, 1H), 4.26-4.35 (m, 4H), 5.02 (m, 1H), 6.07 (m, 1H), 6.83 (d, 2H), 7.22-7.32 (m, 2H), 7.42 (d, 1H), 8.48 (d, 2H). MS: ESP^+ $(M+H)^+ = 371$.

Example 21: (5*R*)- Pyrazin-2-yloxymethyl 3-(4-(4-(6-Cyano-pyridazin-3-yl)piperazin-1-yl)-3-fluorophenyl)-oxazolidin-2-one

Essentially the method of Examples 2 & 3 was used starting from 3-(4-(4-(6-cyano-pyridazin-3-yl)piperazin-1-yl)-3-fluorophenyl)-5(R)-hydroxymethyloxazolidin-2-one (prepared by analogy to Reference Example 1; 240 mg, 0.6 mM) and 2-chloropyrazine (68.7 mg, 0.6 mM). Crude material was precipitated and purified by chromatography on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 2.5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title compound (151 mg).

MS (ESP): 477 (MH^+) for $C_{23}H_{21}FN_8O_3$

NMR (DMSO-d_6) δ: 3.08 (t, 4H); 3.90 (t overlapping m, 5H); 4.18 (t, 1H); 4.53 (dd, 1H); 4.61 (dd, 1H); 5.08 (m, 1H); 7.11 (t, 1H); 7.23 (dd, 1H); 7.40 (d, 1H);

7.53 (dd, 1H); 7.87 (d, 1H); 8.24 (overlapping m, 2H); 8.33 (s, 1H).

Example 22 : (5*R*)- Pyridin-2-yloxymethyl-3-(4-(4-(6-Cyano-pyridazin-3-yl)piperazin-1-yl)-3-fluorophenyl)-oxazolidin-2-one

Essentially the method of Example 21 was used starting from 3-(4-(4-(6-cyano-pyridazin-3-yl)piperazin-1-yl)-3-fluorophenyl)-5(R)-hydroxymethyloxazolidin-2-one (240 mg, 0.6 mM) and 2-fluoropyridine (58.2 mg, 0.6 mM), to give the title compound (54 mg). MS (ESP): 476 (MH^+) for $C_{24}H_{22}FN_7O_3$

NMR (DMSO-d_6) δ: 3.08 (t, 4H); 3.90 (t overlapping m, 5H); 4.16 (t, 1H); 4.47 (dd, 1H); 4.54 (dd, 1H); 5.04 (m, 1H); 6.82 (d, 1H); 7.10 (t, 1H); 7.22 (t, 1H); 7.40 (d, 1H); 7.53 (dd, 1H); 7.87 (d, 1H); 8.24 (overlapping m, 2H); 8.33 (s, 1H).

Example 23 : (5*R*)-(6-Cyanopyridazin-3-yl)oxymethyl-3-(4-(4-(6-cyano-pyridazin-3-yl)piperazin-1-yl)-3-fluorophenyl)-oxazolidin-2-one

Essentially the method of Example 21 was used starting from 3-(4-(4-(6-cyano-pyridazin-3-yl)piperazin-1-yl)-3-fluorophenyl)-5(R)-hydroxymethyloxazolidin-2-one (240 mg, 0.6 mM) and 3-chloro-6-cyanopyridazine (84 mg, 0.7 mM), to give the title compound (60 mg). MS (ESP): 502 (MH^+) for $C_{24}H_{20}FN_9O_3$

NMR (DMSO-d_6) δ: 3.09 (t, 4H); 3.92 (t, 4H); 3.96 (dd, 1H); 4.20 (t, 1H); 4.78 (dd, 1H); 4.85 (dd, 1H); 5.12 (m, 1H); 7.11 (t, 1H); 7.22 (dd, 1H); 7.40 (d, 1H); 7.53 (overlapping m, 2H); 7.88 (d, 1H); 8.24 (d, 1H).

Example 24

The following illustrate representative pharmaceutical dosage forms containing a compound of the formula (I), an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	**Tablet I**	mg/tablet
	Compound X	500
	Lactose Ph.Eur	430
	Croscarmellose sodium	40
	Polyvinylpyrrolidone	20
	Magnesium stearate	10

(b)	**Tablet II**	mg/tablet
	Compound X	100
	Lactose Ph.Eur	179
	Croscarmellose sodium	12
	Polyvinylpyrrolidone	6
	Magnesium stearate	3

(c)	**Tablet III**	mg/tablet
	Compound X	50
	Lactose Ph.Eur	229
	Croscarmellose sodium	12
	Polyvinylpyrrolidone	6
	Magnesium stearate	3

(d)	**Tablet IV**	mg/tablet
	Compound X	1
	Lactose Ph.Eur	92
	Croscarmellose sodium	4
	Polyvinylpyrrolidone	2
	Magnesium stearate	1

(e)	**Capsule**	mg/capsule
	Compound X	10
	Lactose Ph.Eur	389
	Croscarmellose sodium	100
	Magnesium stearate	1

(f) **Injection I**

Compound X	50% w/v
Isotonic aqueous solution	to 100%

(g) **Injection II (e.g. bolus)**

Compound X	10% w/v
Isotonic aqueous solution	to 100%

(h) **Injection III**

Compound X	5% w/v
Isotonic aqueous solution	to 100%

(i) **Injection IV (e.g. infusion)**

Compound X	1% w/v
Isotonic aqueous solution	to 100%

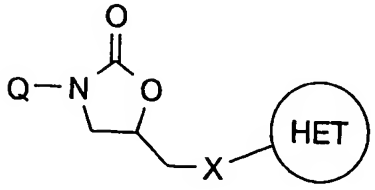
Buffers, pharmaceutically-acceptable surfactants, oils or cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol, glidants (such as silicon dioxide) or complexing agents such as a cyclodextrin (for example, hydroxy-propyl β-cyclodextrin or sulfo-butyl-ether β-cyclodextrin) may be used to aid formulation. Also, improvements in aqueous solubility, if desired, may be achieved, for example, by conjugation of a compound of formula (I) with a phospholipid (such as a (phospho)choline derivative) to form a micellar emulsion.

Note : The above formulations may be obtained by conventional procedures well known in the pharmaceutical art, for example as described in "Remington : The Science & Practice of Pharmacy" Vols. I & II (Ed. A.R.Gennaro (Chairman) et al; Publisher : Mack Publishing Company, Easton, Pennsylvania; 19th Edition - 1995) and "Pharmaceutics - The Science of Dosage Form Design" (Ed. M.E.Aulton; Publisher : Churchill Livingstone; first published 1988). The tablets (a)-(d) may be (polymer) coated by conventional means, for example to provide an enteric coating of cellulose acetate phthalate.

CLAIMS

What is claimed is :

1. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

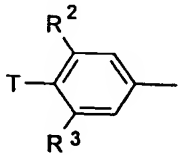


(I)

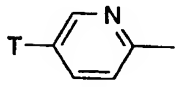
wherein X is -O- or -S-;

HET is a C-linked 6-membered heteroaryl ring containing 1 or 2 N, which ring is optionally substituted on any available C atom (provided that when the N atom is adjacent to the X-link, there is no substitution on any C atom that is adjacent to this N atom) by 1, 2 or 3 substituents independently selected from (1-4C)alkyl, amino, (1-4C)alkylamino, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and halogen;

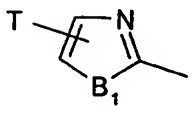
Q is selected from Q1 to Q9 :-



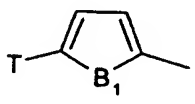
Q1



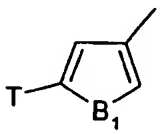
Q2



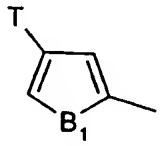
Q3



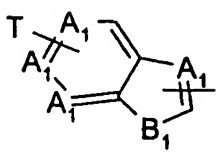
Q4



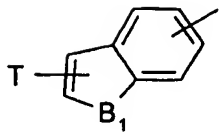
Q5



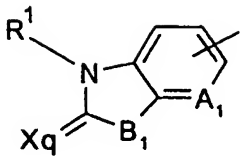
Q6



Q7



Q8



Q9

wherein R^2 and R^3 are independently hydrogen or fluoro;

wherein A_1 is carbon or nitrogen; B_1 is O or S (or, in Q9 only, NH); X_q is O, S or N-R^1 (wherein R^1 is hydrogen, (1-4C)alkyl or hydroxy-(1-4C)alkyl); and wherein

in Q7 each A_1 is independently selected from carbon or nitrogen, with a maximum of 2 nitrogen heteroatoms in the 6-membered ring, and Q7 is linked to T via any of the A_1 atoms (when A_1 is carbon), and linked in the 5-membered ring via the specified carbon atom, or via A_1 when A_1 is carbon; Q8 is linked toT via either of the specified carbon atoms in the 5-membered ring, and linked in the benzo-ring via either of the two specified carbon atoms on either side of the linking bond shown; and Q9 is linked via either of the two specified carbon atoms on either side of the linking bond shown;

wherein T is selected from the groups in (TA) to (TD) below (wherein AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 are defined hereinbelow);

(TA) T is selected from the following groups :-

(TAa) AR1, AR1-(1-4C)alkyl-, AR2 (carbon linked), AR3;

(TAb) AR1-CH(OH), AR2-CH(OH)-, AR3-CH(OH)-;

(TAc) AR1-CO-, AR2-CO-, AR3-CO-, AR4-CO-;

(TAd) AR1-O-, AR2-O-, AR3-O-;

(TAe) AR1-$S(O)_q$- , AR2-$S(O)_q$- , AR3-$S(O)_q$- (q is 0, 1 or 2);

(TAf) an optionally substituted N-linked (fully unsaturated) 5-membered heteroaryl ring system containing 1, 2 or 3 nitrogen atoms;

(TAg) a carbon linked tropol-3-one or tropol-4-one, optionally substituted in a position not adjacent to the linking position; or

(TB) T is selected from the following groups :-

(TBa) halo or (1-4C)alkyl

{optionally substituted by one or more groups each independently selected from hydroxy, (1-4C)alkoxy, (1-4C)alkanoyl, cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, -NRvRw, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2), CY1, CY2 or AR1};

(TBb) -NRv^{1}Rw^1 ;

(TBc) ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl;

(TBd) R^{10}CO- , R^{10}S(O)$_q$- (q is 0, 1 or 2) or R^{10}CS-

wherein R^{10} is selected from the following groups :-

(TBda) CY1 or CY2;

(TBdb) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl, -NRvRw, ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl or 2-(AR2)ethenyl; or

(TBdc) (1-4C)alkyl {optionally substituted as defined in (TBa) above, or by (1-4C)alkylS(O)$_p$NH- or (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N- (p is 1 or 2)};

wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl; Rv^1 is hydrogen, (1-4C)alkyl or (3-8C)cycloalkyl; Rw^1 is hydrogen, (1-4C)alkyl, (3-8C)cycloalkyl, (1-4C)alkyl-CO- or (1-4C)alkylS(O)$_q$- (q is 1 or 2); or

(TC) T is selected from the following groups :-

(TCa) an optionally substituted, fully saturated 4-membered monocyclic ring containing 1 heteroatom selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or sp^3 carbon atom;

(TCb) an optionally substituted 5-membered monocyclic ring containing 1 heteroatom selected from O, N and S (optionally oxidised), and linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom, which monocyclic ring is fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(TCc) an optionally substituted 6- or 7-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a

ring nitrogen atom or a ring sp^3 or sp^2 carbon atom, which monocyclic ring is fully saturated other than (where appropriate) at a linking sp^2 carbon atom; or

(TD) T is selected from the following groups :-

(TDa) a bicyclic spiro-ring system containing 0, 1 or 2 ring nitrogen atoms as the only ring heteroatoms, the structure consisting of a 5- or 6-membered ring system (linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom) substituted (but not adjacent to the linking position) by a 3-, 4- or 5-membered spiro-carbon-linked ring; which bicyclic ring system is

(i) fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(ii) contains one -N(Rc)- group in the ring system (at least two carbon atoms away from the linking position when the link is via a nitrogen atom or an sp^2 carbon atom) or one -N(Rc)- group in an optional substituent (not adjacent to the linking position) and is

(iii) optionally further substituted on an available ring carbon atom; or

(TDb) a 7-, 8- or 9-membered bicyclic ring system (linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom) containing 0, 1 or 2 ring nitrogen atoms (and optionally a further O or S ring heteroatom), the structure containing a bridge of 1, 2 or 3 carbon atoms; which bicyclic ring system is

(i) fully saturated other than (where appropriate) at a linking sp^2 carbon atom;

(ii) contains one O or S heteroatom, or one -N(Rc)- group in the ring (at least two carbon atoms away from the linking position when the link is via a nitrogen atom or an sp^2 carbon atom) or one -N(Rc)- group in an optional substituent (not adjacent to the linking position) and is

(iii) optionally further substituted on an available ring carbon atom;

wherein Rc is selected from groups (Rc1) to (Rc5) :-

(Rc1) (1-6C)alkyl {optionally substituted by one or more (1-4C)alkanoyl groups (including geminal disubstitution) and/or optionally monosubstituted by cyano, (1-4C)alkoxy, trifluoromethyl, (1-4C)alkoxycarbonyl, phenyl (optionally substituted as for AR1 defined hereinafter), (1-4C)alkyl$S(O)_q$- (q is 0, 1 or 2); or, on any but the first carbon atom of the (1-6C)alkyl chain, optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy and fluoro, and/or optionally

monosubstituted by oxo, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylS(O)$_p$NH- or (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N- (p is 1 or 2)};

(Rc2) $R^{13}CO-$, $R^{13}SO_2-$ or $R^{13}CS-$

wherein R^{13} is selected from (Rc2a) to (Rc2e) :-

(Rc2a) AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1, CY2;

(Rc2b) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl,

2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, 2-(AR2a)ethenyl;

(Rc2c) (1-10C)alkyl

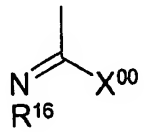
{optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkanoyl and amino; and/or optionally substituted by one group selected from carboxy, phosphonate [phosphono, -P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], phosphoryl [-O-P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylaminocarbonyl, di((1-4C)alkyl)aminocarbonyl, (1-4C)alkylS(O)$_p$NH-, (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)$_p$NH-, fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-, (1-4C)alkylS(O)$_q$-, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-, AR1-S(O)$_q$- , AR2-S(O)$_q$- , AR3-S(O)$_q$- , AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups};

(Rc2d) $R^{14}C(O)O(1-6C)$alkyl wherein R^{14} is AR1, AR2, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (Rc2c)};

(Rc2e) $R^{15}O-$ wherein R^{15} is benzyl, (1-6C)alkyl {optionally substituted as defined for

(Rc2c)}, CY1, CY2 or AR2b;

(Rc3) hydrogen, cyano, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, or of the formula **(Rc3a)**



(Rc3a)

wherein X^{00} is $-OR^{17}$, $-SR^{17}$, $-NHR^{17}$and $-N(R^{17})_2$;

wherein R^{17} is hydrogen (when X^{00} is $-NHR^{17}$and $-N(R^{17})_2$), and R^{17} is (1-4C)alkyl, phenyl or AR2 (when X^{00} is $-OR^{17}$, $-SR^{17}$ and $-NHR^{17}$); and R^{16} is cyano, nitro, (1-4C)alkylsulfonyl, (4-7C)cycloalkylsulfonyl, phenylsulfonyl, (1-4C)alkanoyl and (1-4C)alkoxycarbonyl;

(Rc4) trityl, AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b;

(Rc5) RdOC(Re)=CH(C=O)-, RfC(=O)C(=O)-, RgN=C(Rh)C(=O)- or RiNHC(Rj)=CHC(=O)- wherein Rd is (1-6C)alkyl; Re is hydrogen or (1-6C)alkyl, or Rd and Re together form a (3-4C)alkylene chain; Rf is hydrogen, (1-6C)alkyl, hydroxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkyl, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-4C)alkylamino(2-6C)alkoxy, di-(1-4C)alkylamino(2-6C)alkoxy; Rg is (1-6C)alkyl, hydroxy or (1-6C)alkoxy; Rh is hydrogen or (1-6C)alkyl; Ri is hydrogen, (1-6C)alkyl, AR1, AR2, AR2a, AR2b and Rj is hydrogen or (1-6C)alkyl;

wherein

AR1 is an optionally substituted phenyl or optionally substituted naphthyl;

AR2 is an optionally substituted 5- or 6-membered, fully unsaturated (i.e with the maximum degree of unsaturation) monocyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised;

AR2a is a partially hydrogenated version of AR2 (i.e. AR2 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom if the ring is not thereby quaternised;

AR2b is a fully hydrogenated version of AR2 (i.e. AR2 systems having no unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom;

AR3 is an optionally substituted 8-, 9- or 10-membered, fully unsaturated (i.e with the maximum degree of unsaturation) bicyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

AR3a is a partially hydrogenated version of AR3 (i.e. AR3 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in either of the rings comprising the bicyclic system;

AR3b is a fully hydrogenated version of AR3 (i.e. AR3 systems having no unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom, in either of the rings comprising the bicyclic system;

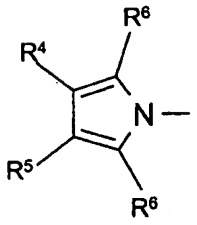
AR4 is an optionally substituted 13- or 14-membered, fully unsaturated (i.e with the maximum degree of unsaturation) tricyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in any of the rings comprising the tricyclic system;

AR4a is a partially hydrogenated version of AR4 (i.e. AR4 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in any of the rings comprising the tricyclic system;

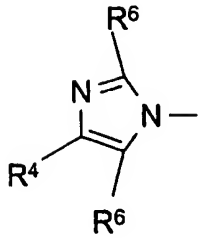
CY1 is an optionally substituted cyclobutyl, cyclopentyl or cyclohexyl ring;

CY2 is an optionally substituted cyclopentenyl or cyclohexenyl ring.

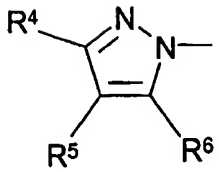
2. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof, as claimed in claim 1 wherein the optionally substituted N-linked (fully unsaturated) 5-membered heteroaryl ring system containing 1, 2 or 3 nitrogen atoms (group (TAf)) is selected from a group of formula (TAf1) to (TAf6) :-



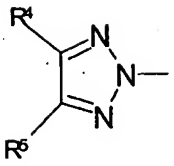
(TAf1)



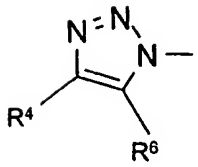
(TAf2)



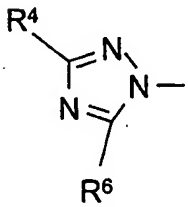
(TAf3)



(TAf4)



(TAf5)



(TAf6)

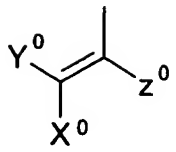
wherein :

R^6 is selected (independently where appropriate) from hydrogen, (1-4C)alkyl, (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, carbamoyl and cyano;

R^4 and R^5 are independently selected from hydrogen, halo, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2), (1-4C)alkanoyl, (1-4C)alkoxycarbonyl, (2-4C)alkanoyloxy-(1-4C)alkyl, benzoxy-(1-4C)alkyl, (2-4C)alkanoylamino, -CONRvRw, -NRvRw and (1-4C)alkyl {optionally substituted by hydroxy, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2), (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONRvRw, -NRvRw; wherein RvRw is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl};

or R^4 is selected from one of the groups in (TAfa) to (TAfc) below, or (where appropriate) one of R^4 and R^5 is selected from the above list of R^4 and R^5 values, and the other is selected from one of the groups in (TAfa) to (TAfc) below :-

(TAfa) a group of the formula (TAfa1)



(TAfa1)

wherein Z^0 is hydrogen or (1-4C)alkyl;

X^0 and Y^0 are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxycarbonyl, halo, cyano, nitro, (1-4C)alkylS(O)q- (q is 0, 1 or 2), RvRwNSO$_2$-, trifluoromethyl, pentafluoroethyl, (1-4C)alkanoyl and -CONRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]; or

one of X^0 and Y^0 is selected from the above list of X^0 and Y^0 values, and the other is selected from phenyl, phenylcarbonyl, -S(O)$_q$-phenyl (q is 0, 1 or 2), N-(phenyl)carbamoyl, phenylaminosulfonyl, AR2, (AR2)-CO-, (AR2)-S(O)q- (q is 0, 1 or 2), N-(AR2)carbamoyl and (AR2)aminosulfonyl; wherein any phenyl group in (TAfa) may be optionally substituted by up to three substituents independently selected from (1-4C)alkyl, cyano, trifluoromethyl, nitro, halo and (1-4C)alkylsulfonyl;

(TAfb) an acetylene of the formula -≡-H or -≡-(1-4C)alkyl;

(TAfc) -X^1-Y^1-AR2, -X^1-Y^1-AR2a, -X^1-Y^1-AR2b, -X^1-Y^1-AR3, -X^1-Y^1-AR3a or -X^1-Y^1-AR3b;

wherein X^1 is a direct bond or -CH(OH)- and

Y^1 is -$(CH_2)_m$-, -$(CH_2)_n$-NH-$(CH_2)_m$-, -CO-$(CH_2)_m$-, -CONH-$(CH_2)_m$-, -C(=S)NH-$(CH_2)_m$- or -C(=O)O-$(CH_2)_m$- ;

or wherein X^1 is -$(CH_2)_n$- or -CH(Me)-$(CH_2)_m$- and

Y^1 is -$(CH_2)_m$-NH-$(CH_2)_m$-, -CO-$(CH_2)_m$-, -CONH-$(CH_2)_m$-, -C(=S)NH-$(CH_2)_m$-, -C(=O)O-$(CH_2)_m$- or -S(O)$_q$-$(CH_2)_m$- ;

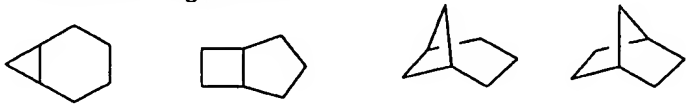
or wherein X^1 is -CH_2O-, -CH_2NH- or -CH_2N((1-4C)alkyl)- and

Y^1 is -CO-$(CH_2)_m$-, -CONH-$(CH_2)_m$- or -C(=S)NH-$(CH_2)_m$- ; and additionally Y^1 is -SO_2- when X^1 is -CH_2NH- or -CH_2N((1-4C)alkyl)-, and Y^1 is -$(CH_2)_m$- when X^1 is -CH_2O- or -CH_2N((1-4C)alkyl)- ; wherein n is 1, 2 or 3; m is 0, 1, 2 or 3 and q is 0, 1 or 2; and when Y^1 is -$(CH_2)_m$-NH-$(CH_2)_m$- each m is independently selected from 0, 1, 2 or 3.

3. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-

hydrolysable ester thereof, as claimed in claim 1 wherein the 7-, 8- or 9-membered bicyclic ring system containing a bridge of 1, 2 or 3 carbon atoms (group (TDb)) is selected from a group defined by the ring skeletons shown in formulae (TDb1) to (TDb14) :-

7-membered ring skeletons



[4,1,0] (TDb1) [3,2,0] (TDb2) [3,1,1] (TDb3) [2,2,1] (TDb4)

8-membered ring skeletons

[3,3,0] (TDb5) [4,2,0] (TDb6) [4,1,1] (TDb7) [3,2,1] (TDb8) [2,2,2] (TDb9)

9-membered ring skeletons

[4,3,0] (TDb10) [5,2,0] (TDb11) [4,2,1] (TDb12) [3,3,1] (TDb13) [3,2,2] (TDb14)

wherein;

(i) the ring system contains 0, 1 or 2 ring nitrogen atoms (and optionally a further O or S ring heteroatom),and when present the ring nitrogen, O or S heteroatom/s are at any position other than as part of the 3-membered ring in (TDb1);

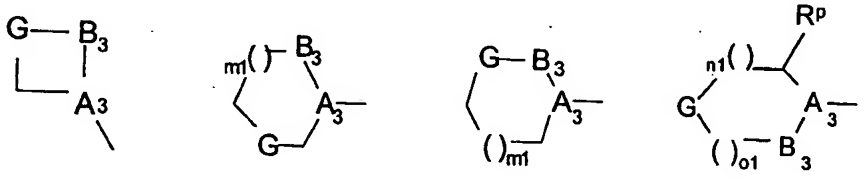
(ii) the ring system is linked via a ring nitrogen atom or a ring sp^3 or sp^2 carbon atom (with the double bond, where appropriate, orientated in either direction) from any position in either ring [other than from a bridgehead position or from an sp^2 carbon atom in the 4-membered ring in (TDb2), (TDb6) and (TDb11)];

(iii) one of the ring carbon atoms at a position not adjacent to the linking position, is replaced (other than when the ring contains an O or S heteroatom) by one of the following

groups -NRc- [not at a bridgehead position], >C(H)-NHRc, >C(H)-NRc-(1-4C)alkyl, >C(H)-CH_2-NHRc, >C(H)-CH_2-NRc-(1-4C)alkyl [wherein the hydrogen atom shown in brackets is not present when the replacement is made at a bridgehead position and wherein a central -CH_2- chain link is optionally mono- or di-substituted by (1-4C)alkyl]; with the proviso that when the ring system is linked via a ring nitrogen atom or an sp^2 carbon atom any replacement of a ring carbon atom by -NRc-, O or S is at least two carbon atoms away from the linking position; and

(iv) the ring system is optionally (further) substituted on an available ring carbon atom as for the bicyclic spiro-ring systems described in (TDa); wherein Rc is as defined in claim 1.

4. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof, as claimed in claim 1 wherein the groups defined in (TCa) to (TCc) are defined by formulae (TC1) to (TC4) :-



(TC1) (TC2) (TC3) (TC4)

wherein in (TC1) : >A_3-B_3- is >C(Rq)-CH(Rr)- and G is -O-, -S-, -SO-, -SO_2- or >N(Rc);

wherein in (TC2) : m1 is 0, 1 or 2; >A_3-B_3- is >C=C(Rr)- or >C(Rq)-CH(Rr)- and G is -O-, -S-, -SO-, -SO_2- or >N(Rc);

wherein in (TC3) : m1 is 0, 1 or 2; >A_3-B_3- is >C(Rq)-CH(Rr)- (other than when Rq and Rr are both together hydrogen) and G is -O-, -S-, -SO-, -SO_2- or >N(Rc);

wherein in (TC4) : n1 is 1 or 2; o1 is 1 or 2 and n1 + o1 = 2 or 3; >A_3-B_3- is >C=C(Rr)- or >C(Rq)-CH(Rr)- or >N-CH_2- and G is -O-, -S-, -SO-, -SO_2- or >N(Rc); Rp is hydrogen, (1-4C)alkyl (other than when such substitution is defined by >A_3-B_3-), hydroxy, (1-4C)alkoxy or (1-4C)alkanoyloxy;

wherein in (TC1), (TC2) and (TC4); m1, n1 and o1 are as defined hereinbefore :

>A_3-B_3- is >N-CH_2- and G is >C(R^{11})(R^{12}), >C=O, >C-OH, >C-(1-4C)alkoxy, >C=N-OH, >C=N-(1-4C)alkoxy, >C=N-NH-(1-4C)alkyl, >C=N-N((1-4C)alkyl)$_2$ (the last two (1-

4C)alkyl groups above in G being optionally substituted by hydroxy) or >C=N-N-CO-(1-4C)alkoxy; wherein > represents two single bonds;

Rq is hydrogen, hydroxy, halo, (1-4C)alkyl or (1-4C)alkanoyloxy;

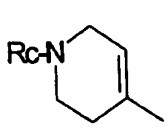
Rr is (independently where appropriate) hydrogen or (1-4C)alkyl;

R^{11} is hydrogen, (1-4C)alkyl, fluoro(1-4C)alkyl, (1-4C)alkyl-thio-(1-4C)alkyl or hydroxy-(1-4C)alkyl and R^{12} is $-[C(Rr)(Rr)]_{m2}-N(Rr)(Rc)$ wherein m2 is 0, 1 or 2;

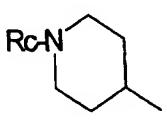
and, other than the ring substitution defined by G, $>A_3-B_3-$ and Rp, each ring system may be optionally further substituted on a carbon atom not adjacent to the link at $>A_3-$ by up to two substituents independently selected from (1-4C)alkyl, fluoro(1-4C)alkyl (including trifluoromethyl), (1-4C)alkyl-thio-(1-4C)alkyl, hydroxy-(1-4C)alkyl, amino, amino-(1-4C)alkyl, (1-4C)alkanoylamino, (1-4C)alkanoylamino-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, AR-oxymethyl, AR-thiomethyl, oxo (=O) (other than when G is >N-Rc and Rc is group (Rc2) defined in claim 1) or independently selected from Rc; and also hydroxy or halo (the last two optional substituents only when G is -O- or -S-);

wherein AR is optionally substituted phenyl, optionally substituted phenyl(1-4C)alkyl, optionally substituted naphthyl, optionally substituted 5- or 6-membered heteroaryl; optionally substituted 5/6 or 6/6 bicyclic heteroaryl ring system, in which the bicyclic heteroaryl ring systems may be linked via an atom in either of the rings comprising the bicyclic system, and wherein both the mono- and bicyclic heteroaryl ring systems are linked via a ring carbon atom and may be (partially) hydrogenated; and wherein Rc is as defined in claim 1.

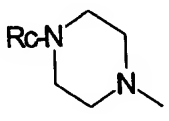
5. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof, as claimed in claims 1 and 4 wherein the groups in (TCa) to (TCc) are defined by formulae (TC5) to (TC11) :-



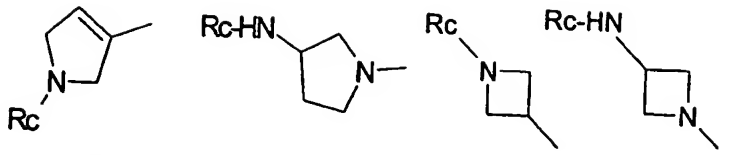
(TC5)



(TC6)



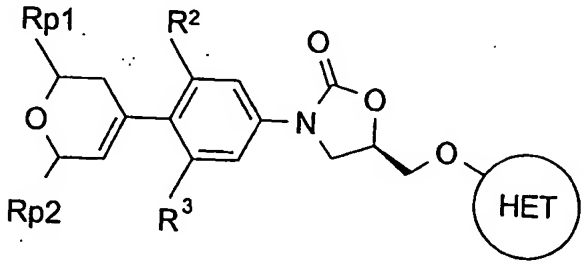
(TC7)



(TC8) (TC9) (TC10) (TC11)

wherein Rc is as defined in claim 1.

6. A compound of the formula (I) as claimed in claims 1 and 4, being a compound of the formula (IB), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof



(IB)

wherein HET is pyridin-2-yl or pyrazin-2-yl (especially pyridin-2-yl); R^2 and R^3 are independently hydrogen or fluoro; and Rp1 and Rp2 are independently hydrogen, hydroxy, bromo, (1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, hydroxymethyl, (1-4C)alkoxymethyl or carbamoyl; or pharmaceutically-acceptable salts thereof.

7. A compound as claimed in claims 1 and 4, being :

5(R)-Pyrid-2-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-(6-Chloropyridazin-3-yloxymethyl)-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Pyrazin-2-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Pyrimidin-4-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Pyridazin-3-yloxymethyl-3-(4-(4-(5-cyanopyrid-2-yl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one;

5(R)-Pyrid-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(4-Methylpyrid-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(3-Methylpyrid-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(6-Chloropyridazin-3-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Pyridazin-3-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Pyrimidin-4-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Pyrazin-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-(5-Chloropyridin-2-yloxymethyl)-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one; or pharmaceutically-acceptable salts thereof.

8. A compound as claimed in claims 1, 4 or 7 being :

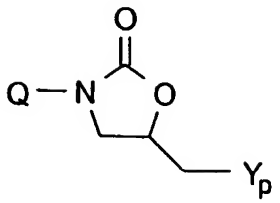
5(R)-Pyrid-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one;

5(R)-Pyrazin-2-yloxymethyl-3-(3-fluoro-4-(3,6-dihydro-(2H)-pyran-4-yl)phenyl)oxazolidin-2-one; or pharmaceutically-acceptable salts thereof.

9. A process for the preparation of a compound of the formula (I) as claimed in claim 1 or pharmaceutically-acceptable salts or *in vivo* hydrolysable esters thereof, which process comprises of **(a)** to **(f)**:-

(a) modifying a substituent in or introducing a substituent into another compound of formula (I);

(b) reacting a compound of formula (II)



(II)

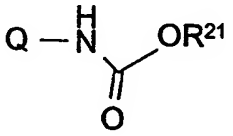
wherein Yp is hydroxy with a compound of the formula (b1) HET-OH or (b2) HET-Lg, wherein Lg is a suitable leaving group;

(c) reacting a compound of formula (II) wherein Yp is a leaving group with a metal alkoxide compound of the formula HET-OM where M is an alkali metal, or another metal known to promote O-alkylation;

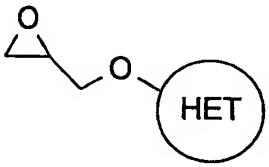
(d) reacting a compound of the formula Q-Zp wherein Zp is an isocyanate or amine group with an epoxide of the formula $CH_2(O)CH\text{-}CH_2O\text{-}HET$;

(e) when X is -S- using a process analogous to process (c) using (e1) a metal thioxide compound of the formula HET-SM where M is an alkali metal, or another metal known to promote S-alkylation; or using (e2) HET-SH and a compound of formula (II) in which Yp is a suitable leaving group;

(f) reacting a urethane compound of formula (III) with a compound of formula (IV)



(III)



(IV)

wherein R^{21} is (1-6C)alkyl or benzyl; and thereafter if necessary :

(i) removing any protecting groups; (ii) forming a pharmaceutically-acceptable salt; (iii) forming an *in vivo* hydrolysable ester.

10. A method for producing an antibacterial effect in a warm blooded animal which comprises administering to said animal an effective amount of a compound of the formula (I) as claimed in claims 1 to 8, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

11. A compound of the formula (I) as claimed in claims 1 to 8, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament.

12. The use of a compound of the formula (I) as claimed in claims 1 to 8, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal.

13. A pharmaceutical composition which comprises a compound of the formula (I) as claimed in claims 1 to 8, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

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A3

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(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: GRAVESTOCK, Michael, Barry [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: BRYANT, Tracey; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

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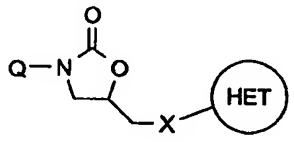
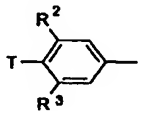
(88) Date of publication of the international search report:
27 January 2000 (27.01.00)

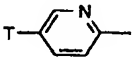
(54) Title: OXAZOLIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)



(Q1)



(Q2)

(57) Abstract

Compounds of formula (I), or a pharmaceutically–acceptable salt, or an in–vivo–hydrolysable ester thereof, wherein, for example, X is –O– or –S–; HET is an optionally substituted C–linked 6–membered heteroaryl ring containing 1 or 2 N atoms; Q is selected from, for example, (Q1) and (Q2); R^2 and R^3 are independently hydrogen or fluoro; T is selected from a range of groups, for example, an N–linked (fully unsaturated) 5–membered heteroaryl ring system or a 3,6–dihydro–(2H)–pyran–4–yl group or a 4–substituted piperazino group; are useful as antibacterial agents; and processes for their manufacture and pharmaceutical compositions containing them are described.

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INTERNATIONAL SEARCH REPORT

	Jonal Application No PCT/GB 99/01737

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D413/14 C07D413/12 A61K31/42 A61K31/44 A61K31/50 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 645 376 A (MERCK PATENT GMBH) 29 March 1995 (1995-03-29) claim 1	1
A	WO 93 23384 A (THE UPJOHN CO.) 25 November 1993 (1993-11-25) cited in the application page 7, line 3 - line 21; claim 1	1-6, 11-13
A	WO 97 09328 A (PHARMACIA & UPJOHN CO.) 13 March 1997 (1997-03-13) cited in the application page 16, line 15 - line 31; claim 1	1-6, 11-13

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 1999	03/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hass, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

ional Application No
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Jonal Application No
PCT/GB 99/01737

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHUNG-HO PARK ET AL: "ANTIBACTERIALS. SYNTHESIS AND STRUCTURE-ACTIVITY STUDIES OF 3-ARYL-2-OXOOXAZOLIDINES. 4 MULTIPLY-SUBSTITUTED ARYL DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 35, no. 6, 1992, page 1156-1165 XP000567006 ISSN: 0022-2623 cited in the application tables I,II	1-6,11, 12
A	W A GREGORY ET AL: "Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidines. 2. The A Group" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 33, 1990, page 2569-2578 XP002082548 ISSN: 0022-2623 cited in the application tables I-VII	1-6,11, 12
A	EP 0 710 657 A (MERCK PATENT GMBH) 8 May 1996 (1996-05-08) claims 1,5-7	1-6,11
A	WO 93 22298 A (TAIHO PHARMACEUTICAL CO LTD.) 11 November 1993 (1993-11-11) abstract	1-6,11
A	WO 94 22857 A (TAIHO PHARMACEUTICAL CO LTD.) 13 October 1994 (1994-10-13) abstract	1-6,11
A	WO 97 06791 A (SCRIPPS RESEARCH INST.) 27 February 1997 (1997-02-27) page 84, compound 15; page 87, compound 16; page 91, compound 17; page 94, compound 18	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01737

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1 (iv) PCT - Method for treatment of the human or animal body by therapy).

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5, 9,11-13 (all partly)

Present claims 1-5, 9, 11-13 relate to an extremely large number of possible compounds and processes for their preparation. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and processes claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out mainly for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claims 6 to 8, the examples disclosed in the description, and their processes of preparation.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/01737

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